EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 June 2022
EMA/622555/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

RAYVOW

International non-proprietary name: lasmiditan

Procedure No. EMEA/H/C/005332/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	RAYVOW
Applicant:	Eli Lilly Nederland B.V. Papendorpseweg 83 3528 BJ Utrecht NETHERLANDS
Active substance:	LASMIDITAN SUCCINATE
International Non-proprietary Name:	lasmiditan
Pharmaco-therapeutic group (ATC Code):	antimigraine preparations, selective serotonin (5ht1) agonists (N02CC)
Therapeutic indication:	Rayvow is indicated for the acute treatment of the headache phase of migraine attacks, with or without aura in adults.
Pharmaceutical form:	Film-coated tablet
Strengths:	50 mg, 100 mg and 200 mg
Route of administration:	Oral use
Packaging:	blister (PCTFE/PVC/alu) and blister (PVC/alu)
Package sizes:	12 x 1 tablets (unit dose), 16 x 1 tablets (unit dose), 2 x 1 tablets (unit dose), 4 x 1 tablets (unit dose) and 6 x 1 tablets (unit dose)

Table of contents

List of abbreviations

5-HT	5-Hydroxytryptamin, serotonin
ADR	Adverse drug reaction
AE	Adverse event
AEOI	Adverse event of interest
AL	Abuse liability
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{0-inf}	Area under the concentration-time curve from time 0 to infinity
AUC_{0-t}	Area under the concentration-time curve from time 0 to time of last quantifiable concentration
AUCtau	Area under the concentration-time curve during one dosing interval at steady state
BAC	Blood alcohol concentration
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BP	Blood pressure
bpm	Beats per minute
CAD	Coronary artery disease
Cave	Geometric mean of time-averaged concentration
CGIc	Clinical Global Impression of Change
CGIs	Clinical Global Impression of Severity
CGRP	Calcitonin gene-related peptide
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent oral clearance
CLR	Renal clearance
Cmax	Maximum plasma concentration
CNS	Central nervous system
CQA	Critical Quality Attribute
CrCl	Creatinine clearance
CRC-MiniSim	Cognitive Research Corporation Driving Simulator-MiniSim
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CVA	Cerebrovascular accident
CVD	Cardiovascular Disease
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DCAE	Discontinuation due to Adverse event
DDI	Drug-Drug interaction
DoE	Design of experiments
EC50	Maximal drug effect
ECG	Electrocardiogram
Emax	Maximum effectiveness
Emin	Minimum effectiveness
EPAR	European Public Assessment Report
EU5	France, Germany, Italy, Spain, United Kingdom
FDA	Food and Drug Administration
FMO	Flavin monooxygenase
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GFR	Glomerular filtration rate
GM	Geometric mean
HA	Headache
HLT	High Level Term

HR	Heart rate
HRQoL	Health-related quality of life
HPLC	High performance liquid chromatography
ICH	Internation Council for Harmonisation
ICP-MS	Inductively coupled plasma mass spectrometry
IHS	International Headache Society
IND	Investigational New Drug
IR	Infrared
ITT	Intent-to-treat
Iv	Intravenous
Ki	Inhibitory constant
LLDPE	Linear Low density polyethylene
LS mean	Least squares mean
LTN	Lasmiditan
MA	Marketing Authorization
MAO	Monoamine oxidase
MATE	Multidrug and toxin extrusion
MBS	Most bothersome symptom
MedDRA	Medicinal Dictionary for Regulatory Activities
MIDAS	Migraine Disability Assessment Test
mITT	Modified intent-to-treat
MQoLQ	Migraine Quality of life Questionnaire
MP	Medicinal product
MS	Member state
NDA	New drug application
NE	Norepinephrine
NIR	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
NOAEL	No observed adverse effect level
NSAID	Nonsteroidal anti-inflammatory drug
OAT	Organic anion transporter
OCT	Organic cation transporter
OLE	Open-label extension (phase)
PBO	Placebo
PBPK	Physiologically based pharmacokinetics
PC	Placebo controlled
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamic
PDE	Permitted Daily Exposure
PGIc	Patient Global Impression of Change
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
popPK	Population pharmacokinetics
PVC	Polyvinyl chloride
PT	Perferred term
QbD	Quality by design
QTc	Corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
Rdnm	Dose normalized ratio
RMP	Risk management plan
SAE	Serious adverse event
SBP	Systolic blood pressure
SCS	Summary of Clinical Safety
SDLP	Standard deviation of lateral position, a measure of weaving while driving in a lane
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA Query
SOC	System organ class
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
TIA	Transient ischemic attack

t½	Elimination Half-life
tmax	Time to maximum concentration
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 6 November 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for RAYVOW, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 March 2019.

The applicant applied for the following indication: "Rayvow is indicated for the acute treatment of migraine with or without aura in adults".

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) (EMEA-002166-PIP01-17) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance lasmiditan contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant did not seek Scientific advice from the CHMP.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	6 November 2020
The procedure started on	26 November 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	15 February 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	18 February 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	1 March 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 March 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 May 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	28 June 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 July 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 July 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	17 August 2021
The CHMP Rapporteurs circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	3 September 2021
The CHMP agreed on a 2nd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on	16 November 2021
The CHMP Rapporteurs circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	1 December 2021

The CHMP agreed on a 3rd list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the CHMP 3rd List of Outstanding Issues on	17 May 2022
The CHMP Rapporteurs circulated the CHMP Rapporteurs Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	8 June 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to RAYVOW on	23 June 2022
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS).	23 June 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Migraine is a serious, chronic, disabling neurological disease characterised by attacks of moderate to severe headache (HA) pain associated with other symptoms such as nausea, vomiting, photophobia, and phonophobia. Migraine attacks typically last from 4 to 72 hours if untreated or unsuccessfully treated. People with migraine may experience an aura prior to the onset of their headache.

2.1.2. Epidemiology

Migraine is a highly prevalent disease, occurring in 11% to 12% of people in Europe, with higher rates among women (16% to 18%) than men (6% to 7%) (Goadsby et al. 2002). The disease is particularly common among individuals between the ages of 25 and 55 years. Migraine has been reported to be the second highest cause of years lived with disability, interfering significantly with occupational, educational, household, family, and social responsibilities (GBD 2017). Because of intense pain and other burdensome symptoms including photophobia, phonophobia, nausea, and vomiting (Linde and Dahlöf 2004; Ford et al. 2017), patients with migraine report extensive limitations in life activities (Leonardi et al. 2010).

People with migraine have higher lifetime rates of comorbid depression, anxiety, panic disorder, sleep disturbances, chronic pain syndromes, and suicide attempts (Buse et al. 2009; MRF 2017). They are also at higher risk for ischaemic stroke and other cardiovascular diseases (Blumenfeld et al. 2011; Sacco and Kurth 2014).

2.1.3. Aetiology and pathogenesis

It is currently thought that migraine has a neurologic aetiology (Goadsby et al. 2002; Goadsby 2009; Amin et al. 2013). The brains of patients with migraine are characterised by a generalised neuronal hyperexcitability, evidenced by increased response to visual, sensory, auditory, and nociceptive stimuli, and migraine attacks involve release of neurotransmitters and activation of pain pathways, including the trigeminal nerve (Xavier et al. 2017; Dodick 2018). Migraine pain appears to involve nociceptive neurons in the dura mater being stimulated and releasing vasoactive neuropeptides such as CGRP. The trigeminal nerve pathway transmits nociception from the meninges via intermediate pathways to the cortex. This neurogenic theory of the pathophysiology of migraine suggests that activation of trigeminal system 5-HT1F receptors might be a useful target for antimigraine drug development (Ramadan et al. 2003; Capi et al. 2017).

2.1.4. Clinical presentation, diagnosis

Standard diagnostic criteria are based the International Classification of Headache Disorders (ICHD-3 beta version). They have been developed by the Headache Classification Committee of the International Headache Society (IHS). As per inclusion criteria in phase 2/3 trials, the target population, for which treatment with LTN is claimed, corresponds to ICHD-3 Codes 1.1 Migraine without aura or 1.2.1 Migraine with typical aura. Accordingly, migraine without aura (1.1) is described as recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the HA are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association

with nausea and/or photophobia and phonophobia. For a firm diagnosis to be established, the patient has to present with at least five attacks, that fulfil a list of respective criteria.

2.1.5. Management

According to current treatment guidelines, unspecific analgesics like acetylic acid, ibuprofen, paracetamol etc. rank among first-line therapies, however, are typically used for less severe migraine attacks. The portion of patients being pain-free 2 hours post-dose is established as the most meaningful measure for efficacy of current migraine therapies. The rates of patients 2-hours pain-free that can be achieved with unspecific NSAIDS in meta-analyses are in the range of 20-25% (Ferrari et al. 2002; Cameron et al. 2015).

Major progress in more specific treatment of acute migraine symptoms was achieved with the advent of the triptans in the nineties. Triptans target 5-HT1B and 5-HT1D receptors and their mechanism is thought to involve cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release. As the gold standard for acute treatment of migraine, they represent 28% to 36% of prescribed acute migraine medications (Mafi et al. 2015; Molina et al. 2018). However, triptans are not efficacious for all patients: rates of pain freedom at 2 hours post-dose with triptans in a meta-analysis are in the range of 20% to 40% (Ferrari et al. 2002). Furthermore, efficacy and tolerability vary, both between agents (7 triptans approved so far), and from patient to patient, with about 30-40% of patients not responding adequately to triptan therapy (Viana M et al. 2013).

Not all patients with migraine tolerate triptans. Among those discontinuing triptan therapy, side effects were reported as the reason in 29% of patients (Wells et al. 2014). Also, triptans are contraindicated in patients with coronary artery disease CAD, peripheral vascular disease, cerebrovascular disease, or uncontrolled hypertension (Dodick et al. 2004; RELPAX SmPC). A large proportion of patients with migraine have cardiovascular risk factors, a history of cardiovascular events, conditions, or procedures, or a high risk of cardiovascular disease (Lipton et al. 2017).

Acute treatment of migraine attacks is to be differentiated from prophylactic treatment of migraine, for which most recently several human / humanised antibodies, selectively binding to the CGRP ligand or its receptor, have been approved.

Although forming the mainstay of current acute migraine therapy, it is concluded that around 30% of patients fail to respond to a particular triptan (Dodick DW 2005). The reasons therefore are not fully understood. On top of considerable inter- and intra-individual attack variability, a large number of other factors modifying responsiveness have been identified, like e.g. concomitant use of preventive medication, medication overuse headache (MoH), inadequate dosing, the time point of medication intake relative to the onset of the attack, incomplete absorption due to concomitant gastric stasis or vomiting, presence resp. absence of aura symptoms etc. (Viana M 2013). Furthermore, the use of the triptans is limited with regard to their cardiovascular (CV) risk profile. As evidenced for the leading substance (sumatriptan), triptans are contraindicated in patients with a previous cerebrovascular accident (CVA), transient ischemic attack (TIA), moderately severe or severe hypertension, or untreated mild hypertension, peripheral vascular disease, established CAD, including ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or Prinzmetal's angina.

Overall, in view of incomplete response to currently available acute migraine medications on the one side and limitations to their use due to CV safety concerns on the other side, there is a general need for new therapeutic approaches in acute migraine therapy. Based on its pharmacological profile as a selective 5-HT1F receptor agonist and the claimed absence of any vasoconstrictive properties, LTN may potentially constitute a valuable contribution to the currently available therapeutic armamentarium.

2.2. About the product

Lasmiditan (LTN) is a new molecular entity. It has been developed by Lilly as LY573144 and by CoLucid Pharmaceuticals, Inc. (CoLucid) as COL-144 and is presented as the first of a new class of selective, high-affinity human serotonin 1F (5-HT1F) receptor agonists – the so-called ditans.

2.3. Type of Application and aspects on development

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended (complete and independent application).

2.3.1. Introduction

The finished product is presented as film-coated tablet containing 50 mg, 100 mg or 200 mg of lasmiditan (as hemisuccinate).

Other ingredients are:

Tablet core: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, pregelatinized starch and sodium laurilsulfate

Film coating: polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, talc, iron oxide black (E172) and iron oxide red (E172) (100 mg tablet only).

The product is available in polychlorotrifluoroethylene/polyvinyl chloride (PCTFE/PVC) and polyvinyl chloride (PVC) perforated unit dose blisters sealed with an aluminium foil lid.

2.3.2. Active Substance

General information

The chemical name of lasmiditan is 2,4,6-trifluoro-N-(6-(1-methylpiperidine-4-carbonyl)pyridine-2-yl)benzamide corresponding to the molecular formula $C_{19}H_{18}F_3N_3O_2 \cdot 0.5[C_4H_6O_4]$. It has a relative molecular mass of 436.41 g/mol (377.36 g/mol for lasmiditan free base) and the following structure:

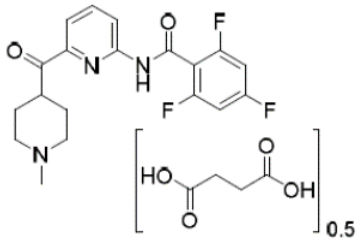


Figure 1: Active substance structure

The chemical structure of lasmiditan was elucidated by a combination of elemental analyses, FT-IR spectroscopy, NMR spectroscopy and mass spectrometry. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), X-ray crystallography and solid-state NMR spectroscopy among further methods.

Following salt-screening, the hemisuccinate salt was selected based on solid-state properties and high aqueous solubility.

Lasmiditan hemisuccinate is a white to practically white powder and is non-hygroscopic.

Lasmiditan has a non - chiral molecular structure.

Polymorphism has been observed for the active substance. The yielded form has been shown to be thermodynamically stable in long term stability studies under long-term, intermediate and accelerated conditions.

The particle size of the active substance is controlled in the specification to ensure good manufacturability.

Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site. Lasmiditan hemisuccinate is synthesized using well defined starting materials with acceptable specification.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The manufacturing process includes two isolated intermediates, for which acceptable specifications were set.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Eight previous synthetic routes were used before the proposed Route 9 emerged. The synthetic routes differ with respect to starting materials, number of isolated intermediates and reagents used. Changes introduced have been presented in sufficient detail and have been justified. Batch data and impurity profiles of batches used for formulation development, stability and clinical trials are comparable with respect to their impurity profile.

QbD principles were followed during development of the process. For each operation, a risk assessment was conducted considering the CQAs identity, potency, and purity. Process parameters of each manufacturing step (i.e., charge amounts, temperature, time) are controlled at proven acceptance ranges (PARs). A discussion whether the synthetic process is sensitive to scale has been provided, and it has been confirmed that the findings of the parametric studies are applicable to commercial scale.

The degradation chemistry of lasmiditan is well understood and based on forced degradation studies.

A genotoxic risk assessment in line with ICH M7 was conducted for the starting materials and their synthesis impurities, as well as for the impurities formed during each manufacturing step covering potential process impurities, by-products, reagents, and solvents. It has been confirmed that possible mutagenic/carcinogenic impurities are purged to levels less than their acceptable intake based on the TDI of the active substance. The proposed limits for individual potential genotoxic impurities have been confirmed by analytical results generated with full scale batches. The proposed control strategies are appropriate and justified.

The primary packaging material complies with the EC directive EC 10/2011 as amended and with monograph Ph. Eur 3.1.3. for polyolefins.

Specification

The active substance specification includes tests for: identity (IR), crystal form (XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), genotoxic impurities (HPLC/MS), Palladium (ICP), description, particle size (laser diffraction), loss on drying (Ph. Eur.) and residue on ignition (Ph. Eur.).

The specification limits for the active substance have been set in line with ICH Q6A (R2). The characteristics relevant for the manufacturability and pharmaceutical effectiveness are adequately specified.

Limits for all other impurities have been set in line with ICH Q3A.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 6 batches manufactured with a synthetic route equivalent to the commercial route of synthesis were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability studies were conducted using primary batches of the active substance manufactured using synthetic Route 8, which is equivalent to the proposed commercial Route 9.

Stability data from three batches of active substance stored in the intended commercial package for up to 24 months under long term conditions (30ºC / 65% RH) and for up to six months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: description, assay (dried basis), impurities, identity, crystal form, loss on drying, and package characteristics (a check of the integrity of the packaging components). In addition to these properties, additional tests were performed for information purposes. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications and no specific trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. No significant degradation was observed for solid state samples exposed to simulated sunlight.

Results on stress conditions were also provided. Solid samples of active substance were stressed with heat (70 °C) at both low and high humidity (20 % and 75% RH). No significant degradation occurred.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored between 1-30°C in the proposed container.

2.3.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as film-coated tablets containing lasmiditan (as succinate) as active substance. Three strengths are proposed to be authorised:

- 50 mg: light grey, oval tablet of 8.9 x 4.9 mm, debossed with "4312" on one side and "L-50" on the other.

- 100 mg: light purple, oval tablet of 11.2 x 6.15 mm, debossed with "4491" on one side and "L-100" on the other.
- 200 mg: grey, oval tablet of 14.1 x 7.75 mm, debossed with "4736" on one side and "L-200" on the other.

The three strengths can be sufficiently differentiated by colour, size and debossing.

The aim of formulation and manufacturing process development was to achieve a rapid release of the active substance and to ensure robust manufacture of a patient-friendly dosage form. The use of high shear wet granulation successfully addressed sticking issues observed during preliminary formulation screening studies and improved the flow properties of formulations containing a high percentage of the lasmiditan active substance. A film coat was used to improve appearance and administration of the tablet. Sufficient information on pharmaceutical development has been presented.

The impact of the particle size of the active substance has been sufficiently discussed and particle size is controlled in the active substance specification. Chemical stability of lasmiditan tablets is not affected by the form conversion and tablets remain rapidly dissolving during stability storage.

Results from compatibility studies of the excipients with the active substance have been presented and compatibility has been overall sufficiently demonstrated. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards with the exception of the colourants. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Sufficient information on the composition and manufacturing of each batch used during clinical studies has been presented. The Phase 1 to 3 clinical program and registration stability studies initially used white round tablets in the same strengths as the commercial tablet of 50, 100 and 200 mg, respectively (designated 'T1'). The formulation used during clinical studies is the same as that intended for marketing. The commercial tablets ('T2') have the same core tablet composition and manufacturing process, but differ in colour, shape and embossment.

The dissolution of the finished product has been studied. Dissolution testing of finished product tablets was conducted in three media spanning the physiological pH range. In all cases, dissolution is very rapid, meeting the criteria of >85% dissolved at 15 minutes.

Sufficient information on manufacturing development has been provided. For each manufacturing step, a design space has been evaluated across small scale batches, pilot batches and commercial scale batches. The design space for each step is based on an initial risk assessment and leads to an upscaling of the initial risk evaluation. As an outcome of all studies performed, an overall design space of the manufacturing process has been provided.

The primary packaging is polychlorotrifluoroethylene/polyvinyl chloride (PCTFE/PVC) perforated unit dose blisters sealed with an aluminium foil lid or polyvinyl chloride (PVC) perforated unit dose blisters sealed with an aluminium foil. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of seven main steps: granulation, final blend, extra granular powder blend and final blend lubrication as well as tablet compaction, film coating and packaging of coated tablets have been addressed. The process is considered to be a standard manufacturing process.

The design space has been developed across small scale batches, pilot batches and commercial scale batches. Scale independent parameters have been selected to describe the design space.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

A holding time has been defined for the bulk coated tablets.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including identification (IR), potency (HPLC), purity (HPLC), description (visual), uniformity of dosage units (Ph. Eur.), disintegration (Ph. Eur.), dye identity (chemical) and microbial testing (Ph. Eur.).

The release specification and shelf-life specification include all relevant parameters to control the finished product.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches of each strength using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

Following the first round of assessment, a major objection was raised in relation to the nitrosamines. Based on the additional data and information presented in response, a major objection was satisfactorily resolved. A risk assessment concerning the potential presence of nitrosamine has been performed in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 5 commercial-scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability studies were conducted with both T1 and T2 finished product according to the ICH guidelines. The T1 tablets and commercial T2 tablets have the same core tablet composition and manufacturing process, as well as coating system (PVA based) and differ only in the shape and the colour (T1 tablets are round and white) (see above for more details).

Primary stability batches of T1 tablets manufactured at a manufacturing site different from the commercial manufacturing site and packaged in PCTFE/ PVC laminated blisters were stored under long term conditions (25 ºC / 60% RH) and under accelerated conditions (40 ºC / 75% RH). Stability data for

5 batches each of the 50 and 100 mg tablets and 4 batches of the 200 mg tablets are available for up to 36 months at the long-term and up to 6 months at accelerated storage conditions.

Batches of T2 tablets packaged in PCTFE/PVC laminated blisters and PVC blisters were stored under long term conditions (30ºC/65% RH) and under accelerated conditions (40 ºC / 75% RH). Data for one batch each of the 50 and 100 mg tablets are available up to 24 months at long-term and up to 6 months at accelerated storage conditions for. These batches were manufactured at pilot scale at a manufacturing site different from the commercial manufacturing site. Data for 3 batches each of the 50 and 100 mg and 200 mg tablets packaged in PCTFE blisters and PVC blisters manufactured at the commercial manufacturing site and at commercial scale are available up to 24 months at long-term and 6 months at accelerated storage conditions.

Samples were tested for identification, potency, purity, description, disintegration and microbial purity. The analytical procedures used are stability indicating.

No significant trend was observed under any of the storage conditions. The results from both the long-term and accelerated data show little or no overall change in dissolution over time.

In addition, a photostability study using T2 finished product was conducted on one batch each of 50, 100 mg and 200 mg tablets and samples were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results demonstrate that the finished product is photostable.

Stress tests have been conducted and one batch each of 50 mg, 100 mg and 200 mg tablets. Samples were exposed to multiple temperature and humidity combinations to assess the chemical stability of the formulation. The tablets were exposed to 70°C/20% RH and 70°C/75% RH for 21 days. No degradation products were observed above the reporting threshold (0.05%) after 7, 14 and 21 days at any of the stress condition, demonstrating that the finished product is chemically stable.

Based on available stability data, the proposed shelf-life of 3 years and without any special storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, a Major Objection was raised in relation to the nitrosamines. Satisfactory responses were received to resolve the Major Objection.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were two minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, which pertain to the reviewing of assay limits for the active substance and providing the 6 months stability results for an impurity in the finished product; these are put forward and agreed as recommendations for future quality development.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

Lasmiditan (also referred to as LY573144 or COL-144) is claimed to be a high-affinity, highly selective 5-HT_{1F} receptor agonist that is being developed as a novel therapy for the acute treatment of migraine attacks in adult patients and is claimed not to cause vasoconstriction.

Overview of the Non-clinical Testing Strategy

For all pivotal safety pharmacology and toxicology studies, lasmiditan was administered as the hemisuccinate salt, which is the same form used clinically and intended for commercial marketing.

The clinical development and submission for registration of lasmiditan for acute treatment of migraine is supported by a comprehensive non-clinical program including: primary, secondary, and safety pharmacology; pharmacokinetic (absorption, distribution, metabolism, and excretion); and toxicology assessments.

Species selection
The primary pharmacodynamics/non-clinical efficacy of lasmiditan was determined in rat models of trigeminal nerve activation. Conventional non-clinical species were used for studies of safety pharmacology: the mouse to evaluate behavioural and CNS functions; the rat to evaluate respiratory and renal function; and the dog to evaluate cardiovascular function. General toxicology studies were conducted in rats and dogs. Rats and rabbits were used in the developmental and reproduction studies. The potential for carcinogenicity was tested in the rat and in the rasH2 transgenic mouse. The potential for drug abuse was studied in rats. These species are pharmacologically relevant (lasmiditan binds to 5-HT_{1F} receptors in humans and in these non-clinical species with high selectivity and potency) and metabolically relevant (metabolic pathways in these species are similar to those in humans) models for human safety assessment.

Dose selection
Doses for the pharmacodynamic studies were chosen to evaluate a full range of dose-response activity that was considered to include both primary and secondary effects. Consistent with regulatory guidance [for example, ICH M3(R2)], the high doses for toxicity studies were selected to provide substantial challenge to the test animals and cause systemic pharmacological and toxic effects. Low doses were selected to provide no-observed-effect and/or no-observed-adverse-effect levels (NOEL, NOAEL).

Route of administration
Lasmiditan was initially developed as an IV formulation, however, it was ultimately developed for oral administration. The safety pharmacology studies were performed early in the development of the molecule and, therefore, employed the IV route of administration. Toxicology studies employed both

routes of exposure, although pivotal toxicology studies were conducted by the oral route of administration. No major qualitative differences could be observed in the plasma profiles of metabolites when comparing these different routes of administration; thus, studies conducted by both routes provide data relevant for assessment of human risk.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

In vitro and *in vivo* studies have been conducted to characterize the primary pharmacodynamics of lasmiditan.

Table 1 Primary pharmacodynamic studies performed with lasmiditan

Type of study / Study ID	Test system	Route
Radioligand binding assays / CNS571	Cloned human 5-HT receptors	*In vitro*
Radioligand binding assays and cAMP functional assays / CLP-005c	Cloned human 5-HT receptors	*In vitro*
Radioligand binding assays of Lasmiditan and metabolites / CLP-002e-HTR	Human, mouse, rat, dog, and rabbit serotonin receptors	*In vitro*
[^{35}S]GTPγS binding assay of functional activity / CNS558	Cloned human 5-HT1 receptors	*In vitro*
Radioligand binding assays of Lasmiditan metabolites / PM73	Cloned human 5-HT receptors	*In vitro*
Stimulation-induced dural plasma protein extravasation / CNS574	Rat, Wistar	IV and oral
Stimulation-induced dural plasma protein extravasation / NS22	Rat, Sprague Dawley	Oral
Stimulation-induced c-Fos expression / CNS549	Rat, Sprague Dawley	Oral
Trigeminovascular nociception / Goadsby- Holland-TCC	Rat, Sprague Dawley	IV
KCl-stimulated CGRP release from ex-vivo dura mater, trigeminal ganglion, and trigeminal nucleus caudalis / NS23-EUMC2- amdt-01	Mice, C57BL/6J	*Ex-vivo*
Vasodilation of dural artery induced by electrical stimulation and capsaicin / NS23-EUMC2-amdt-01	Rat, Sprague Dawley	IV
Transient cephalic and hindpaw allodynia / NS-32- MAYOCLINIC	Rat, Sprague Dawley	Oral

***In vitro* data**

Receptor-binding studies

Cloned human 5-HT_{1F} receptors

Lasmiditan demonstrated high affinity binding to human cloned 5-HT_{1F} receptors and a high degree of selectivity compared to all other evaluated 5-HT receptor subtypes, including the 5-HT_{1B} receptor that has been associated with the vasoconstrictive properties of the triptans.

According to receptor-binding data obtained in studies CNS571 and CLP-005c, the K_i of lasmiditan for the cloned human 5-HT_{1F}-receptor amounts to 2.2 respectively 1.8 nM. For specific comments concerning the clinical relevance of these data, see Day 80 Non-Clinical AR and section 3.2.5.

In receptor-binding studies, lasmiditan metabolites (including the major human metabolites M7, M8, and S,R-M18) were practically inactive at the cloned human 5-HT_{1F} and all other evaluated 5-HT receptor subtypes.

Cloned 5-HT_{1F} receptors and other 5-HT receptor subtypes from various species

In vitro receptor-binding studies showed also a high affinity of lasmiditan for cloned mouse, rat, rabbit and dog 5-HT_{1F} receptors.

Measured IC_{50}-values amounted to 1.29 nM (mouse), 3.32 nM (rat), 1.57 nM (rabbit), 13.3 nM (dog) and 4.87 nM (human). The observed numerical differences in IC_{50}-values were considered to reflect assay variability but not real species-differences in binding affinity of lasmiditan. Metabolites of lasmiditan showed weak to no binding to cloned mouse, rat, rabbit and dog 5-HT_{1F} and all other evaluated 5-HT receptor subtypes.

Functional assays

Lasmiditan showed potent agonistic effects at cloned human 5-HT_{1F} receptors and a high selectivity versus functional effects mediated via other 5-HT receptor subtypes.

The EC_{50} value for 5-HT_{1F}-mediated inhibition of forskolin-stimulated cAMP formation of cultured cells amounted to 3.74 nM. In addition, the functional selectivity of lasmiditan for the 5-HT_{1F} receptor versus the 5-HT_{1B} receptor, thought to be involved in vasoconstrictive effects, was >2600 fold. In contrast, the EC_{50} values for the evaluated triptan molecules at the 5-HT_{1B} receptor are all less than 85 nM, indicating potent functional effects.

The EC_{50} value for 5-HT_{1F}-mediated stimulation of [^{35}S]GTPγS binding to membrane G-proteins amounted to 43 nM.

***In vivo / ex vivo* data**

Animal models assumed to reflect aspects of human migraine disease

Trigeminal nerve activation has been implicated in pathogenesis of human migraine disease. Efficacy of lasmiditan was demonstrated in different rat and mouse models of trigeminal nerve activation, that are considered to reflect aspects of human migraine disease:

- Lasmiditan inhibited trigeminal stimulation-induced plasma protein extravasation in the dura.
- Lasmiditan inhibited trigeminal stimulation-induced cFos expression in the trigeminal nucleus caudalis.
- Lasmiditan inhibited trigeminovascular nociception (evaluated dose 5 mg/kg); and blocked the release of CGRP.

Effective doses of lasmiditan in these models varied considerably and were highly dependent on the experimental assay conditions. This is further discussed in section 3.2.5.

Lasmiditan inhibited vasodilation of the dural artery induced by electrical stimulation and capsaicin (effective doses amounted to 0.3 mg/kg or higher, corresponding to a HED of ≥ 0.05 mg/kg or a total dose of ≥ 2.5 mg for a person weighing 50 kg) , but not by exogenous CGRP.

Other data

Repeated administration of lasmiditan promoted transient cephalic and hindpaw allodynia that could be reinstated with stress or nitric oxide donor. The potential relevance of this model for Medication Overuse Headache is discussed in section 3.2.5.

2.4.2.2. Secondary pharmacodynamic studies

Secondary PD non-GLP studies have been conducted with lasmiditan and lasmiditan metabolites *in vitro* on non-targeted receptors, ion channels and transporters and *in vivo* on non-targeted organs.

Based on studies of target selectivity, it is concluded that lasmiditan and its metabolites are not expected to have significant off-target (other than 5-HT_{1F} receptor related) activity.

In vitro data

Binding studies

In radioligand binding studies, lasmiditan showed a high degree of selectivity for the 5-HT_{1F} receptor versus the other evaluated 5-HT receptor subtypes.

In screening studies involving radioligand binding assays, affinity of lasmiditan and its major human metabolites to a panel of neurotransmitter- and brain/gut peptide-related receptors were evaluated. The Applicant concludes that,

- with the exception of the $GABA_A$ benzodiazepine site no appreciable binding was observed;
- lasmiditan is not expected to interfere with physiologic/pathophysiologic functions mediated by e.g. histamine, dopamine D_1 and D_2, adrenergic or muscarinic receptors.

Furthermore, lasmiditan and its metabolites did not display relevant affinity for recombinant human and rat CB1 and CB2 receptors and for the human dopamine transporter, data suggesting a low risk for cannabinoid receptor-mediated or dopamine-mediated drug abuse potential.

Functional assays

Lasmiditan and its major human metabolites were not agonists, antagonists or positive allosteric modulators at different isoforms of the $GABA_A$ subunit.

In vivo/Ex vivo data

Effects on tone of blood vessels

In *ex vivo* studies, lasmiditan did not induce constriction of the rabbit saphenous vein and of multiple human arteries (internal mammary, proximal or distal coronary, or middle meningeal).

In vivo, lasmiditan did not change coronary or carotid artery diameter in anesthetized beagle dogs.

The triptan sumatriptan was included in all of these studies and did, in accordance with the known vasoconstrictive properties of triptans (that have been associated with activation of 5-HT_{1B} receptors) induce constrictions of all the evaluated vessels.

The lack of vasoconstrictive effects observed for lasmiditan clearly differentiates it from the triptan class of compounds presently used for the acute treatment of migraine attacks.

2.4.2.3. Safety pharmacology programme

Overview

Safety pharmacology studies were performed to assess potential effects of IV administered lasmiditan on cardiac, CNS, respiratory, and renal function.

Table 2 Safety pharmacology studies performed with lasmiditan

Type of study/ study ID / GLP status	Test system	Main findings

Cardiovascular ion channel / *Study LLY01_21* /GLP no	HEK 293 cells transfected with hERG clone Lasmiditan 0.1, 0.3, 1, 3, 10, 100 µM	Inhibition of hERG current IC_{50} = 3.1 µM
Cardiovascular ion channel / *Study 100127.DME*/GLP no *Study 090731.DME* /GLP yes	HEK 293 cells transfected with hERG clone (S,S)-M18:10, 30, 100 µM M7, (S)-M8: 10, 30, 100, 300 µM (S,R)-M18: 10, 30 µM	M7 and (S)-M8 weakly inhibited hERG with IC_{50} of 129.8µM and 40.2 µM, respectively. IC_{50} could not be determined for (S,R)-M18 and (S,S)-M18 (> 30 and 100 µM, respectively
Cardiovascular function / *Study DV0302 /* GLP yes	Dog, beagle Lasmiditan hemisuccinate 0.6, 2, 6 mg/kg IV infusion	NOAEL: 6 mg/kg 6 mg/kg: ↑HR (12 bpm; 10%) 20 min to 120 min postdose
CNS function / *Study PN0216 /* GLP no	Mouse, CD-1 1, 4, 12 mg/kg IV bolus	NOEL: 4 mg/kg 12 mg/kg: ↓ambulatory activity (15 min postdose), ↓nonambulatory activity (15 and 30 min postdose)
CNS function / *Study PN0216 /* GLP yes	Mouse, CD-1 0.1 (auditory only), 1, 4, 12 mg/kg IV bolus	NOEL (other effects): 4 mg/kg NOEL (auditory only): <0.1 mg/kg Dose ≥0.1 mg/kg: ↑auditory sensorimotor reactivity to auditory startle At 12 mg/kg: ↓writhes, ↓qualitative activity (5 and 30 min postdose), ↓ core BT (5 and 30 min postdose), ↑convulsive threshold
Respiratory function / *Study MN103025 /* GLP yes	SD Rat Lasmiditan hemisuccinate 1, 4, 12 mg/kg IV infusion	No effect up 12 mg/kg NOEL: 12 mg/kg
Renal function / *Study R04902 /* GLP yes	Rat, Fischer 344 Lasmiditan hemisuccinate 1, 4, 12 mg/kg IV bolus	NOEL: <1 mg/kg Dose ≥1 mg/kg: ↑urine pH, ↑urine solute and electrolyte excretion (osmoles, sodium, potassium, and chloride), ↑urine dilution, ↓urine osmolality

Changes in various parameters were observed, however, overall, the totality of the safety pharmacology and related toxicology data suggest a low potential for lasmiditan related adverse effects on cardiovascular, respiratory, or renal function at clinically relevant exposures.

While CNS signs have been reported in clinical trial subjects, the potential for serious CNS effects (for example, convulsions) at the proposed clinical dose of 200 mg is low. Estimated exposure multiples to the human C_{max} at a dose of 200 mg is provided in the Table below (see also data for repeat dose toxicity).

Table 3 Cmax Exposures and Animal:Human Cmax Multiples for Safety Pharmacology Parameters

Safety Pharmacology Study	NO(A)EL (mg/kg, IV)	C_{max} (ng/mL)	Exposure Multiple[a]
Human, 200 mg, oral[b]	-	260	-
Cardiovascular safety pharmacology in conscious dogs (DV0302)	6	1277[c]	4.9
CNS safety pharmacology in mice (PN0216 and PN0217)	4[d]	No Exposure Data Available	-
Respiratory pharmacology in rats (MN103025)	12	894[e]	3.4
Renal pharmacology in rats (R04902)	12	894 [e]	3.4

Abbreviations: NO(A)EL = No Observed (Adverse) Effect Level
a Exposure multiple = Cmax (human/animal).
b Population Pharmacokinetic Analysis of Study: H8H-BD-LACA, H8H-CD-LAHS, H8H-CD-LAHQ, H8H-CD-LAHR, H8H-CD-LAHP, H8H-CD-LAHG, H8H-CD-LAHH, H8H-CD-LAHN, H8H-CD-LAHF, H8H-CD-LAHI, H8H-MC-LAHA, H8H-MC-LAHB, H8H-MC-LAHC, H8H-MC-LAHE, H8H-MC-LAHD, H8H-MC-LAHT, H8H-MC-LAHU, H8H-CD-LAHM and Concentration-Response Analysis of Study: H8H-CD-LAHM.
c Estimated based on Day 1 Cmax values (male + female) from Study 57494.
d For CNS signs excepting effect on auditory stimulus.
e Estimated based on Day 1 Cmax values (male + female) from Study 57493.

Cardiovascular function

In vitro data

hERG studies

In vitro hERG studies of lasmiditan (or lasmiditan metabolites) suggest limited liability for effects on the QT_c interval at a plasma $C_{max,u}$ associated with the proposed maximum clinical dose of 200 mg. The clinical C_{max} of unbound (free) lasmiditan ($C_{max,u}$) was approximately 10-fold less than the IC_{50} concentration at the hERG channel.

Human metabolites were less potent for inhibition of the hERG channel compared to lasmiditan, and in-vitro hERG IC_{50} values were greater than 40-fold the clinical Cmax,u of the metabolites at clinical lasmiditan doses ranging up to 400 mg (Hazell et al. 2017).

In vivo data

IV safety pharmacology study in dogs using telemetry evaluations

In a safety pharmacology study in conscious dogs using telemetry devices, there were no important effects on cardiovascular function after single IV doses up to 6 mg/kg (considered by the Applicant as NOAEL), corresponding to an exposure of unbound lasmiditan ($C_{max,u}$) greater than 5-fold higher than unbound exposure at a human dose of 200 mg (see Table below).

Repeat dose toxicity studies in dogs using telemetry evaluations

ECG evaluations using surface electrodes in restrained animals were included in repeated dose toxicology studies in dogs.

Effects on cardiac action potential

- 2-week IV study: There were no lasmiditan-related alterations in ECG assessments at doses up to 15 mg/kg.
- Oral 14-day pilot study: A potential for QT prolongation at very high exposure was suggested by

higher QTc values in the 60-mg/kg females and a trend to higher QTc values in the 90-mg/kg males.

- Oral 4- and 13-week studies: No lasmiditan-related ECG findings were reported at doses up to 60 mg/kg and 50 mg/kg, respectively.
- Oral 39-week study: ECG changes (increases in QRS, QT and QTc intervals) were reported at the high dose of 50 (reduced to 40) mg/kg/day in association with $C_{max,u}$ exposures approximately 14-fold higher than the 200-mg human dose.

Table 4 Exposure Multiples of hERG IC50 or Dog Cmax,u Relative to Human Cmax,u

	$C_{max, total}$ (ng/mL)	**$C_{max,u}$ (ng/mL)**	**Ratio hERG IC_{50} or Dog $C_{max,u}$:Human $C_{max,u}$** [b]
Human, 200 mg [a]	260	117	-
hERG study IC_{50} (ng/mL) [b]	NA	1170	10.0
Dog (cardiovascular safety study) 6 mg/kg IV [c]	1277	741	6.3
Dog (39-week toxicology study) 50/40 mg/kg PO [d]	2776	1610	13.8

Abbreviations: Cmax, total = mean total maximum plasma concentrations; Cmax,u = mean unbound maximum plasma concentrations; hERG = human ether-à-go-go-related gene; IC50 = half maximal inhibitory concentration; IV = intravenous; NA = not applicable; PO = oral.

a Human: Population Pharmacokinetic Analysis of Study: H8H-BD-LACA, H8H-CD-LAHS, H8H-CD-LAHQ, H8H-CD-LAHR, H8H-CD-LAHP, H8H-CD-LAHG, H8H-CD-LAHH, H8H-CD-LAHN, H8H-CD-LAHF, H8H-CD-LAHI, H8H-MC-LAHA, H8H-MC-LAHB, H8H-MC-LAHC, H8H-MC-LAHE, H8H-MC-LAHD, H8H-MC-LAHT, H8H-MC-LAHU, H8H-CD-LAHM and Concentration-Response Analysis of Study: H8H-CD-LAHM. Human fu=0.45. The mean unbound maximum plasma concentrations (Cmax,u) for humans is 117 ng/mL (0.3 μM)

b hERG: Study LLY 01_21.

c Dog: Cardiovascular safety pharmacology study (DV0302); Exposure estimated based on average of male + female Cmax, total on Day 1 from Study 57494.

d Dog: 39-week toxicology study (8204494): average of male + female Cmax, total at Week 39, dog fu=0.58.

At 400 mg (twice the maximum recommended daily clinical dose), lasmiditan does not delay cardiac repolarization/prolong QT interval in the clinical thorough QT study (TQT) in healthy volunteers (COL MIG-105/H8H-CD-LAHP.

Effects on heart rate

In the cardiovascular safety pharmacology study in instrumented dogs, heart rate was slightly higher (12 beats per minute) 20 to 120 minutes after IV dose administration. Additionally, in a vasoconstriction study in anesthetized dogs, heart rate in the lasmiditan treatment group appeared stable over the course of the study, and no significant changes from baseline were observed.

In clinical pharmacology studies, lasmiditan has been associated with a transient lowering of heart rate based on data across the clinical pharmacology program.

Other cardiovascular parameters

Following IV injection of doses up to 6 mg/kg in dogs there were no compound-related effects on blood pressure or left ventricular inotropic state.

The totality of the data suggests a low potential for lasmiditan-or lasmiditan metabolites to elicit adverse effects on cardiovascular function in humans at clinically therapeutic plasma concentrations.

Respiratory function

Lasmiditan did not affect respiratory function in rats.

CNS function

Lasmiditan is a centrally penetrant drug, and the CNS was identified as a target organ in the nonclinical safety studies.

IV safety pharmacology study in mice:

IV administration of lasmiditan was associated with signs of both excitation (e.g., increased sensitivity to auditory stimuli) and, at high doses (e.g., 12 mg/kg IV) CNS depression (e.g., hypoactivity, decreased ambulatory activity, increased seizure threshold).

Oral repeat dose toxicity studies

C_{max}-related clinical signs of CNS toxicity (e.g., ataxia, tremors, and, convulsions) were observed at high doses in all species in the toxicology studies. However, signs such as convulsions occurred at C_{max} exposures well above (>10-fold) those associated with human therapeutic levels (see Repeat dose toxicity.

Although treatment-emergent balance disorder and tremor were observed in the clinical development program, treatment-emergent seizures have not been observed.

Renal function

In the rat renal safety pharmacology study, compound-related effects on renal function consisted of minimal-to-slight increases in urine pH, urine solute excretion, and production of dilute urine following IV administration of lasmiditan.

2.4.3. Pharmacokinetics

The disposition of lasmiditan has been studied in mice, rats, rabbits, and dogs, which are the species used in pharmacology and toxicology studies.

Lasmiditan was administered IV to rats, rabbits, and dogs and orally to mice, rats, rabbits, and dogs in single and repeat-dose studies to evaluate the PK/TK of lasmiditan and lasmiditan metabolites.

Absorption

IV application

In repeat-dose studies by IV administration, lasmiditan exposure increased with dose in a generally proportional manner in rats and dogs. The apparent elimination half-life in both species on Day 14 was approximately 2 to 4 hours. There were no significant sex differences in exposure and no evidence of accumulation after 14 days.

Oral application

Single dose - Rat

In rats, lasmiditan was well absorbed. The absolute bioavailability of lasmiditan was 64% for males and 58% in females. The elimination half-life ($t_{1/2}$) of lasmiditan in plasma was 2 to 3 hours whereas the $t_{1/2}$ of radioactivity was 27 to 32 hours. Combined biliary and urinary recoveries in bile duct-cannulated rats indicated that at least 76% of the oral dose was absorbed.

Single dose - Dog

In dogs, lasmiditan was well absorbed. The absolute bioavailability was 63% for males and 36% for females. The $t_{1/2}$ of lasmiditan was 3 to 8 hours whereas the $t_{1/2}$ of radioactivity was 56 to 85 hours.

Food had relatively little effect on overall exposure of lasmiditan in dogs, although it delayed t_{max} from 1.25 to 3.5 hours.

Multiple dose – Mouse, rat, rabbit, dog

Exposure: In oral repeat-dose studies, the exposure of lasmiditan and several monitored metabolites [M3, M7, M8, (S,S)-M18, and (S,R)-M18)] increased with dose in a generally proportional manner in mice, rabbits, and dogs. The increase in exposure was less than proportional in rats. Accumulation was observed at some doses in rats and in rabbits but not in mice or dogs. The metabolite-to-parent AUC ratios for all evaluated metabolites were independent of dose and sex in all species. There were no consistent sex-related exposure differences for lasmiditan and metabolites in any species.

t_{max}: In mice, rats, and dogs, lasmiditan was rapidly absorbed, with t_{max} generally ≤1 hour.

Elimination half-life: The apparent elimination half-life of lasmiditan after oral administration was approximately 2 to 3 hours in rats and approximately 8 hours in dogs, whereas the $t_{1/2}$ of radioactivity was much longer in both species (27 to 85 hours).

Distribution

Tissue distribution

[^{14}C]Lasmiditan was widely distributed in rats. In albino rats, the highest concentrations of total radioactivity were measured in the urinary bladder and liver, with lung, Harderian glands, and kidney showing levels of total radioactivity higher than blood. In pigmented rats, the highest concentrations of radioactivity were found in the uveal tract of the eye, suggesting binding to melanin.

Intact lasmiditan crossed the blood-brain barrier of rats as evidenced by brain-to-plasma ratios of approximately 3 over the 24-hour time course after IV and oral dosing. A rat brain quantitative whole-body autoradiography (QWBA) study with [^{14}C]lasmiditan demonstrated that the highest concentrations of radioactivity were found in pituitary gland, pineal gland, and cerebrospinal fluid.

Protein binding

Protein binding of lasmiditan in plasma of mouse, rat, and dog ranged from 42% to 55%. Protein binding in monkey plasma ranged from 86% to 90%.

Placental transfer

In pregnant rats, [^{14}C]lasmiditan-related material (lasmiditan and metabolites) crossed the placenta and radioactivity was measurable in all fetal tissues at the final sampling time of 24 hours postdose.

Metabolism

Lasmiditan was extensively metabolized *in vitro* and *in vivo* to numerous metabolites, with significant overlap in metabolic pathways between species.

In vivo, [^{14}C]lasmiditan was extensively biotransformed to numerous metabolites, with lasmiditan accounting for <20% of circulating radioactivity in rats and dogs.

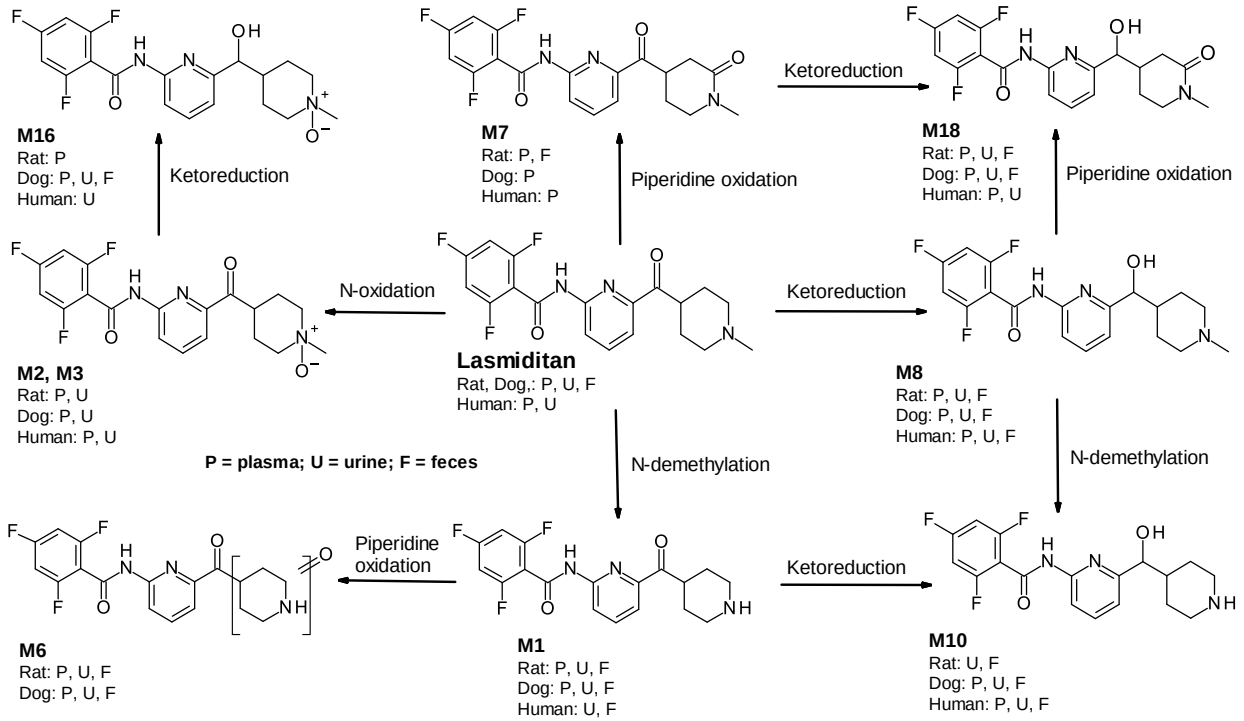
The major biotransformation pathway for rats and dogs based on recovered dose was N-demethylation to M1. The major circulating metabolite in mice, rats, and dogs was the N-oxide (M2 – trans isomer, M3 – cis isomer), whereas the major circulating metabolite in rabbits was the reduced ketone (M8). Other animal metabolites observed in plasma and/or excreta included M7 (oxidation on the piperidine ring) and various combinations of all these identified pathways (M6, M10, M16, and M18).

Three primary metabolites (M3, M7, and M8) and two downstream metabolites ([S,R]-M18 and [S,S]-M18) were measured in repeat-dose studies. Biotransformation of lasmiditan to M8 and M18 introduced chiral centers and the (S)-isomer of M8 predominated in all species. Species-specific differences in abundance of (S,R)-M18 versus (S,S)-M18 diastereomers were noted.

Metabolites M7, M8, (S,R)-M18, and (S,S)-M18 were designated as major circulating human metabolites and were all detectable in plasma of mice, rats, rabbits, and dogs. The completed toxicology studies have adequately assessed these metabolites and safety coverage of the major human metabolites has been demonstrated.

Metabolite M3 was the primary circulating metabolite in mouse, rat, and dog whereas M8 was the most abundant circulating metabolite in rabbit. M1 was the major excreted metabolite in rats and dogs.

Figure 2 Major metabolism pathways of lasmiditan in rats and dogs.



P: plasma, U: urine, F: feces

Excretion

Urine and bile

Overall recovery of [^{14}C]lasmiditan in rats was >90% and 76% to 88% in dogs. After oral and IV administration, the majority of radioactivity was excreted in the urine in both species. In rats, biliary excretion amounted to 28% of an orally administered dose. Significant concentrations of radiocarbon in feces following IV administration of [^{14}C]lasmiditan suggest that biliary excretion is involved in dog as well.

Renal elimination was the major route of excretion of drug-related material in humans although unchanged lasmiditan only accounted for approximately 2% to 3% of the dose. These results indicate that the overall disposition of lasmiditan in rats and dogs was similar between species and representative of the human disposition of the compound.

Breast milk

[^{14}C]Lasmiditan-related radioactivity was excreted into the milk of lactating rats with a milk-to-plasma ratio of 3.3 over a 24-hour time course.

Pharmacokinetic drug interactions

No drug-drug interaction studies have been conducted in animals.

2.4.4. Toxicology

Lasmiditan was evaluated in a comprehensive series of toxicology studies in laboratory animals and in *in-vitro* test systems to support clinical use. The non-clinical testing program was, in general, consistent with current relevant international regulatory guidelines [e.g. ICH M3(R2)].

Lasmiditan was initially developed as an IV formulation, however, it was ultimately developed for oral administration. Toxicology studies employing both routes of exposure were presented for completeness. No major differences could be observed in the plasma profiles of metabolites when comparing different routes of administration.

Overall, the collective results of the toxicology studies provide evidence for the non-clinical safety profile of lamiditan and its major human metabolites [M3, M7, M8, [S,R]-M18, [S,S]-M18, were qualified within the context of many toxicology studies] and provide exposure data that allow to establish safety margins (exposure multiples) to the MRHD of 200 mg.

Single dose toxicity

Lasmiditan treatment was associated with CNS related clinical signs including tremors, ataxia, hypoactivity, recumbency, head shaking, clonic movements, and convulsions.

Convulsions and/or mortality occurred only at oral or IV doses associated with high C_{max} values (generally >3000 ng/mL), for example following oral doses of 120 mg/kg in dogs, ≥100 mg/kg in rats, and 300 mg/kg in mice. The highest tolerated single oral dose in dogs was considered to be 60 mg/kg.

Repeat dose toxicity

Rat studies

Oral 13-Week Study with 4-Week Recovery

Lasmiditan doses of 0, 10, 30, 50, 100, or 200 mg/kg were administered daily for 13 weeks via oral gavage. Control, 100 mg/kg and 200 mg/kg groups underwent additional 4 weeks of recovery. Important finding included the following:

- Lasmiditan was generally well tolerated at doses of ≤ 30 mg/kg in males and ≤ 50 mg/kg in females.
- Kidney findings indicative of adverse renal toxicity were seen in males given ≥ 50 mg/kg and females given ≥ 100 mg/kg.
- Males given ≥50 mg/kg showed reversible, minimal to slight centrilobular hepatocyte vacuolation.
- Nonreversible clinical pathology effects included higher urine volume and lower urine specific gravity for males given ≥100 mg/kg and lower total protein, albumin, and albumin-to-globulin ratio for females given 200 mg/kg.
- The NOAEL for lasmiditan was considered to be 30 and 50 mg/kg in males and females, respectively, corresponding to C_{max} values of 1180 ng/mL and 1480 ng/mL and $AUC_{0\text{-}24\ hr}$ values of 11450 ng•hr/mL and 19080 ng•hr/mL, respectively, at Week 13.

Oral 26-Week Study with 8-Week Recovery

Lasmiditan doses of 0, 10, 30, 50, 100, or 200 mg/kg were administered daily for 26 weeks via oral gavage. Control, 100 mg/kg and 200 mg/kg groups underwent additional 8 weeks of recovery. Important finding included the following:

- Lasmiditan was generally well tolerated at doses ≤ 50 mg/kg.
- Mortality occurred at 200 mg/kg.
- CNS-related clinical signs (myoclonic jerking, convulsions) occurred in one control and one 100-mg/kg rat and with a higher frequency in two animals at 200 mg/kg.
- Pigmentary inclusions were observed in the cytoplasm of large motor neurons of the brain stem and spinal cord of rats given ≥100 mg/kg. The toxicologic relevance is unclear. The inclusions were not associated with degenerative changes in affected neurons or surrounding nerve tissue and were not correlated with CNS-related clinical signs.
- Non-reversible effects on urinary concentrating ability (decreased urine specific gravity) in males and females at ≥100 mg/kg were observed in conjunction with an exacerbation of background renal pathology indicative of chronic progressive nephropathy in males at ≥100 mg/kg and females at 200 mg/kg.
- Increased heart weights and degenerative cardiomyopathy was evident in males given 200 mg/kg and females given ≥100 mg/kg. These changes were interpreted by the Applicant as test article-related exacerbations of species-specific spontaneously-occurring background conditions.
- Cardiomyopathy, renal effects, and intracellular inclusions in CNS neurons were still evident after an 8-week recovery period.
- The Applicant considered that the NOAEL was 50 mg/kg, corresponding to a C_{max} of 1619 ng/mL and an $AUC_{0\text{-}24hr}$ of 18404 ng•hr/mL (males and females combined) at Week 26.

Dog studies

13-Week Study with 4-Week Recovery

Beagle dogs received daily oral doses of 0, 5, 10, 20, and 50 mg/kg lasmiditan for 13 weeks. Control and high dose groups also underwent 4 weeks of recovery. Important finding included the following:

- Lasmiditan at dose levels up to 50 mg/kg resulted in no deaths
- Systemic toxicity occurred mainly in animals given 50 mg/kg lasmiditan and included vomitus/emesis, CNS-related clinical signs (tremors, twitching, hypoactivity), reduced mean

body weight, and decreased mean body weight gain (substantial in females, modest in males) and food consumption compared with controls.

- Most of these effects were transient, and only the reduced body weight gain and CNS-related clinical signs in animals receiving the 50 mg/kg dose were, according to the Applicant, considered adverse.
- According to the Applicant, the 20 mg/kg dose was considered to be the NOAEL and corresponded to a C_{max} of 1686 ng/mL and an $AUC_{0\text{-}24hr}$ of 11416 ng•hr/mL (males and females combined) at Week 13.

39-Week Study with 8-Week Recovery

Beagle dogs (Cohort 1) received daily oral doses of 0, 5, 10, 20, and 50/40 mg/kg for 39 weeks. A second cohort of dogs (Cohort 2) was added to incorporate additional groups administered 0 or 30 mg/kg. The control and high dose groups also underwent 8 weeks of recovery.

- Lasmiditan at dose levels up to 50/40 mg/kg resulted in no test article-related deaths.
- However, lasmiditan was associated with adverse clinical signs at 50/40 mg/kg, particularly CNS-related clinical sign of tremors which was most frequently observed from 1 to 2 hours postdose, coinciding with the t_{max} for lasmiditan.
- Administration of lasmiditan was associated with prolongation of the QTc interval and increased QRS duration in animals given 50/40 mg/kg. However, increased QT instability was not observed; therefore, the lengthening of the QTc was considered by the Applicant not to represent a signal favoring torsadogenicity.
- Clinical and anatomic pathology changes attributed to lasmiditan were not considered adverse by the Applicant based on their low severity, absence of obvious clinical correlates, and complete or partial reversibility.
- Based on the incidence, frequency, and severity of clinical signs, particularly, tremors, 30 mg/kg was considered by the Applicant to be the NOAEL, which corresponded to a lasmiditan C_{max} of 2319 ng/mL and $AUC_{0\text{-}24hr}$ of 15368 ng•hr/mL (males and females combined) at Week 39.

Overview of safety margins (exposure multiples) derived from toxicity studies

According to the Applicant adequate margins of safety were derived from the non-clinical NOAELs and clinical exposure at the maximum proposed dose of 200 mg lasmiditan.

These exposure margins can be considered somewhat conservative in nature, because the proposed clinical dosing regimen is not daily, as opposed to the daily dosing regimen employed in the nonclinical studies.

Table 5 Exposures and Margins of Safety for Lasmiditan Following Oral Administration of 200 mg to Humans

Species	Dose (mg/kg)	Dose (mg/m^2)	C_{max} (ng/mL)[a]	MOS	AUC (ng•hr/mL)[a,b]	MOS
Human[b]						
200 mg/70 kg	2.9	107	260	NA	1770	NA
Mouse[c]						
NOAEL	200	600	5932	23	55525	31
Rat[d]						
NOAEL	30	180	1180	4.5	11450	6.5
Dog[e]						
NOAEL	30	600	2319	8.9	15368	8.7
Rat EFD[f]						
NOAEL	175	1050	3827	15	64823	37
Rabbit EFD[g]						
NOAEL	75	900	964	3.7	2614	1.5
Rat PPND[h]						
NOAEL	150	900	3291 (est)	>10 (est)	55748 (est)	>30 (est)

Note: Margins of safety are derived from NOAELs in pivotal oral toxicology studies.
Abbreviations: AUC = area under the concentration-versus-time curve; Cmax = maximum measured plasma concentration; est = estimated; GD = gestation day; MOS = margin of safety; NA = not applicable; NE = Not Evaluated; NOAEL = no-observed-adverse-effect level.
Dose (mg/kg) * X = Dose (mg/m2) where X = 3, 6, 12, 20, and 37 for mouse, rat, rabbit, dog, and human, respectively (FDA 2005).
a Data are combined for male and females. Human AUC0-inf; Animal AUC0-24hr.
b Population Pharmacokinetic Analysis of Study: H8H-BD-LACA, H8H-CD-LAHS, H8H-CD-LAHQ, H8H-CD-LAHR, H8H-CD-LAHP, H8H-CD-LAHG, H8H-CD-LAHH, H8H-CD-LAHN, H8H-CD-LAHF, H8H-CD-LAHI, H8H-MC-LAHA, H8H-MC-LAHB, H8H-MC-LAHC, H8H-MC-LAHE, H8H-MC-LAHD, H8H-MC-LAHT, H8H-MC-LAHU, H8H-CD-LAHM and Concentration-Response Analysis of Study: H8H-CD-LAHM.
c Mouse 13-week oral study (7874-126), Week 13 (highest dose tested = NOAEL = 200 mg/kg).
d Rat 13-week oral study (7874-116), Week 13 (highest dose tested = 200 mg/kg; NOAEL males = 30 mg/kg).
e Dog 39-week oral study (8204494), Week 39 (highest dose tested = 50/40 mg/kg; NOAEL = 30 mg/kg).
f Rat embryo-fetal development study (8213912) Gestation Day 17 (highest dose tested = 250 mg/kg; NOAEL = 175 mg/kg).
g Rabbit embryo-fetal development study (8223068) Gestation Day 20 (highest dose tested = 115 mg/kg; NOAEL = 75 mg/kg).
h Rat pre-/postnatal development study (8220236) (highest dose tested = 225 mg/kg; NOAEL = 150 mg/kg) Exposure was estimated based on toxicokinetic data from rat EFD study (8213912) and assuming linearity of dose-exposure relationship.

Acute or repeated exposure to lasmiditan in the toxicology studies was associated with CNS-related clinical signs including hypoactivity, tremors, ataxia, recumbency, head shaking, clonic movements and convulsions.

These signs progressed in severity as dose (and thus, C_{max} exposures) increased. Convulsions and/or mortality occurred only at exposures associated with high oral doses and exposures as shown in the Table below and generally occurred 1 to 2 hours postdose. C_{max} exposures were greater than 10-fold above human C_{max} values at the 200-mg oral dose (260 ng/ml for total lasmiditan plasma levels).

Table 6 Lowest Observable Effect Doses and Cmax Concentrations Associated with Mortality and Convulsions Following Oral Dosing with Lasmiditan in Nonclinical Species

Species	Study	LOEL for Mortality (# Animals; Day of Death)	LOEL for Convulsions (# Animals; Day)	C_{max} (ng/mL) (Time Point)
Mouse	7874-112	300 mg/kg (5/5 M; Day 1)	300 mg/kg (10/sex[a], Day 1)	15450 (Day 1)
Rat	B01-217	250 mg/kg (2/5 F; Days 6, 9) 100 mg/kg (1/5 F; Day 11)[b]	250 mg/kg (1/5F; Days 3 and 6 within 1 hr postdose)	4650 (Day 1) 2810 (Day 13)
Rat	8202968	200 mg//kg 2/16 M, Days 12, 89; 3/16 F, Days 22, 148, 178)	200 mg/kg[c] (1/16 M, 1/16 F; during dosing and recovery phases)	M+F combined: 3374 (Week 13) 3025 (Week 26)
Dog	7874-101	120 mg/kg (1/2 M;1/2 F, Day7)	120 mg/kg (1/2 M, 1/2 F; Day 7, at 0.8-1.3 hr postdose)	M: 9130, F: 7318 (Day 7)
Dog	7874-109	-	60 mg/kg (myoclonic jerking) (1/5 F; Day 2, 1-2 hr postdose)	F H05812: 5150 ng/mL (Day 1)

Abbreviations: F = female; hr = hour; LOEL = lowest observable effect level; M = male.
a All animals given 300 mg/kg were sacrificed in a moribund condition
b A single female given 100 mg/kg was found dead in the morning of Day 11. No changes in body weight or food and water consumption, and no clinical signs were observed in this animal before death.
c The relationship of these clinical signs to test article could not be ascertained due to their spontaneous occurrence in 1 control animal and the low number of 100-mg/kg animals affected; however, the higher frequency of observations at 200 mg/kg suggested test article-related exacerbation of a spontaneously occurring condition.

Genotoxicity

Lasmiditan was negative in in vitro Ames tests, a chromosome aberration assay (CHO cells) and two in vivo micronucleus test following oral, respectively intravenous administration performed in mice.

For the in vivo micronucleus test following intravenous application no PK data was submitted by the applicant. Based on the TK data obtained in in vivo micronucleus test following intravenous treatment

at 125 mg/kg (MD), multiples of exposures are expected ~ 28 x for C_{max} and ~ 29 x for AUC to the human clinical exposure at 200 mg (C_{max} 260 ng/ml, AUC 1770 ng h/ml).

In addition, clinical signs noted in both assays were consistent with that observed in in the 4 week repeat dose toxicity study (8302173) in mice.

No statistically significant increase in the number of micronucleated PCE's as compared to the vehicle and no cytotoxicity (bone marrow) could be observed in both studies in any treatment group.

In conclusion, lasmiditan is not considered to be genotoxic under the conditions of the studies.

Carcinogenicity

Carcinogenicity testing of lasmiditan was carried out in a 2 year lifespan study in Crl:CD(SD) rats and a 6 month study in hemizygous Tg.rasH2 mice in compliance with GLP.

2 year lifespan study in Crl:CD(SD) rats:

Neoplasms detected in the long-term study in rats seemed not to be related to the treatment of lasmiditan. All neoplastic alterations observed were reported in the literature or exhibited either no dose relationship, were within the range of the historical control incidences (Charles River Laboratories Ashland), or were common or spontaneous neoplasms in aged rats. Compared to the clinical exposure

at 200mg, multiples of exposures were 4.1 x and 5.4 x for male and 9.9 x and 18.3 x for female rats based on C_{max} and AUC_{last}

However, an analysis of the data submitted by the Applicant for the unscheduled, early deaths in this study showed, that the lasmiditan doses of 10, 25 and 75 mg/day dose were associated with an earlier occurrence of unscheduled deaths, specifically, of deaths due to pituitary neoplasms in male animals (as reflected by a left-shift in the respective Kaplan-Meier survival curves). This issue is further discussed in section 3.2.5.

6 month study in hemizygous Tg.rasH2 mice

In the mouse study, bronchiolo-alveolar carcinomas/adenomas were observed in females in the high dose group (12%) and an increased combined incidence of bronchiolo-alveolar carcinoma and adenoma (16%) versus control was detected. These findings were not considered as treatment-related by the applicant.

Despite a common tumour in Tg.rasH2 mice, based on the study report it appears that animals from the positive group (treated with MNU) did not developed any bronchiolo-alveolar carcinoma but this was mostly observed in mice treated with Lasmiditan. In addition, based on Madhav G Paranjpe et.al (Int J Toxicol. Jan-Feb 2013; 32(1):48-57), the combined incidence of 16% observed in females (HD group) is above the 7.74% average value reported. Moreover, a BAC value of 12% is also above the value reported by Nambiar et al (2012): lung bronchiolo-alveolar adenocarcinomas (mean 1.4-2.4%; range 0-5%). This issue is further discussed in section 3.2.5.

Reproductive and developmental toxicity

In a rat fertility and early embryonic development study, with doses up to 200 mg/kg lasmiditan there were no adverse effects on reproductive parameters (mating, fertility, and fecundity indices) at any dose.

A slight increase in the number of females with extended periods of metestrus/diestrus occurred at doses ≥50 mg/kg. However, as there was no correlation between females with irregular cycles and any mating or fertility parameters, these differences were not considered adverse. Although a negative lasmiditan relationship on male fertility cannot be excluded, due to the drug holiday of 3 days in the high dose group, it seems unlikely because of the short half-live and additional no effects on reproductive organs were seen in the long term carcinogenicity study.

The no observable adverse effect level (NOAEL) for parental toxicity is 100 mg/kg/day for both males and females. The NOAEL for fertility and early embryonic development was 250/200 mg/kg/day for males and 200 mg/kg/day for females, the highest dose tested. This corresponds to margins of safety for fertility of 13 x for male and 17x for female rats at a NOAEL of 200 mg/kg.

Embryo-fetal development toxicity studies were conducted in rats and rabbits. Lasmiditan caused developmental toxic effects in both rats and rabbits. The effects were decreased fetal body weight with associated delayed skeletal ossification. At the high doses, the maternal toxicity was also significant, included clinical signs of toxicity, and decreased body weight or body weight gain and food consumption. A slight increase in postimplantation loss (attributed to two dams with severe maternal toxicity) was seen in the rabbit. A low incidence of fetal cardiovascular (ventrical septal) defects were observed in the high dose group of the rabbit dosed orally in one of the conducted EFD studies. In the second oral EFD study and in the IV study in the rabbit no cardiovascular defects were seen. However, a lasmiditan relationship cannot be excluded.

In the oral embryo-fetal development study conducted in rabbits, one fetus was reported with meningocele and corresponding absent skull bones at the high dose level of 115 mg/kg/day. Although it

is acknowledged that drug-related toxicity was observed in the dam producing this litter and, in the litter, this point was further discussed by the Applicant (see 3.2.5), and the SPC 5.3 amended accordingly.

Overall, it can be concluded that the developmental and reproductive effects occurred only at doses associated with maternal toxicity. At the no adverse effect level for embryo-fetal development, systemic exposure levels were 8-fold (rat) and 1.5-fold (rabbit) the human exposure at therapeutic dose levels.

Exposure to lasmiditan from implantation to weaning induced maternal toxicity (reduction of body weight gain and food consumption) at ≥150 mg/kg/day. Pregnancy or gestation indices, gestation length, number of live pups, number of resorption and birth index were also affected by doses of 225 mg/kg/day. This is approximately at a 50-fold higher exposure than the human exposure at 200 mg. Prolonged gestation and parturition and an increased number of stillborn pups and frequency of postnatal death occurred. In the high dose group, pups had reduced growth rates during the lactational period. This corresponded with lack of milk in the pups' stomachs and underdevelopment of the maternal mammary gland. The pups continued to have reduced body weights relative to controls through adulthood. Locomotor activity, auditory and pupillary reflex acquisition, learning, memory and reversal learning, and reproductive performance were unaffected by treatment. There was a significant reduction in the mean number of delivered pups and live pups in the high dose (225 mg/kg), corresponding with a reduction in implantation sites for F1 females after mating. The clinical relevance of these effects should be discussed. Placental transfer and subsequent fetal exposure to [^{14}C] lasmiditan related radioactivity occurred at moderate levels through 24 hours postdose. [^{14}C] lasmiditan was excreted into the milk of lactating rats, with a resulting milk-to plasma AUC ratio of approximately 3. The NOAEL for the developmental effects at 150 mg/kg/d gives a safety margin of >10 (C_{max}) or 30 fold (AUC) at a human dose of 200 mg/d.

Other toxicity studies

Immunotoxicity

According to Guideline ICH S8 "Immunotoxicity studies for human pharmaceuticals", all new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity. A weight of evidence review should be performed on information from all available studies to determine whether a cause for concern exists. No such data had been initially provided by the Applicant. This issue is further discussed in section 3.2.5.

Dependence - Drug Abuse Potential

Lasmiditan treatment was associated with neurobehavioral signs of sedation and hypoactivity in a CNS safety pharmacology study in mice and in the repeat-dose toxicology studies.

Nonclinical studies of abuse liability demonstrated that:

- Lasmiditan did not generalize to the benzodiazepine lorazepam (drug discrimination study [VPT4730]),
- Lasmiditan, unlike the benzodiazepine chlordiazepoxide, was not associated with physical dependence (drug withdrawal study [VPT5005]).
- Lasmiditan was weakly self-reinforcing in a self-administration study in rats, similar to the benzodiazepine diazepam (RS1732).

The IV self-administration study design was compliant with regulatory guidance and expectations ("Guideline on the Non-Clinical Investigation of the Dependence Potential of Medicinal Products" EMEA/CHMP/SWP/ 94227/2004; "Assessment of Abuse Potential of Drugs Guidance for Industry" FDA 2017;) and was further optimized using a Fixed Reinforcement schedule of 3 (FR3) to provide near

maximum sensitivity for detecting any type of signal. In addition, two benzodiazepine comparators were used due to the known weak reinforcing nature of benzodiazepines in general (see Smith et al. 2017).

Lasmiditan met the criteria for a positive reinforcer at the highest unit dose of 0.8 mg/kg/injection, as the mean number of infusions (9.5 injections per session) was (i) greater than the predetermined background rate of 6 injections per session and (ii) statistically higher than 5.0 injections per session for saline (Figure 2.6.6.1), whereas the two lower doses of lasmiditan (0.5 and 0.2 mg/kg/injection) were not statistically significant reinforcing (mean number of lasmiditan infusions 4.5 and 6.5, respectively).

Thus, lasmiditan was found to be weakly reinforcing at the highest unit dose tested in heroin-maintained rats. The mean number of injections per session for the 0.8 mg/kg/injection lasmiditan group was similar to that of the high dose of diazepam which is known to be a weakly reinforcing drug in humans and laboratory animals, while it was significantly lower than that for heroin which is known to be a strongly reinforcing drug in humans and laboratory animals and is a well-known drug of abuse in humans.

According to the Appliant, the IV self-administration study is considered to have high predictivity with regard to reinforcing activity in humans (Horton et al. 2013). In fact, the results of the nonclinical self-administration study are consistent with those of the human abuse potential study (H8H-MC-LAHB). In the clinical study, the highest lasmiditan dose tested exhibited drug liking similar to alprazolam. The results of the human abuse potential study are described in the proposed product label.

Studies on impurities

Non-genotoxic impurities: Nonclinical studies support the proposed specifications of no more than (NMT) 0.3% total impurity (Section 3.2.S.4.1) based on margins of safety (≥1) achieved in key toxicology studies relative to the proposed clinical dose of 200 mg.

Genotoxic impurities: Consistent with the recommendations of ICH M7(R1), a complete assessment of genotoxic impurities in the commercial synthetic route was conducted.

Studies on metabolites

Metabolite safety was qualified in the non-clinical repeat dose toxicity studies.

Other studies

Phototoxicity

Lasmiditan was distributed in uveal tract of the eye and skin and exhibited affinity for melanin in pigmented rats with maximum absorptions of lasmiditan in the UV-vis spectrum (225, 255 and 298 nm). In the *in vitro* 3T3 NRU phototoxicity test using Balb/c 3T3 mouse fibroblasts lasmiditan was not phototoxic under the conditions of the study.

Nevertheless, based on the study report it was initially not completely clear if the study was conducted at standard settings (UVA filter >320 nm) or if modified irradiation settings were included to better fit the absorption spectra of lasmiditan in the lower (UVB) range of the UV visible spectrum. On request, the Applicant has confirmed that the study was conducted in accordance with ICH guideline S10 and it has been agreed that no additional phototoxicity testing is considered necessary Lasmiditan is photostable and to date no case of phototoxicity was detected under clinical settings.

2.4.5. Ecotoxicity/environmental risk assessment

The applicant provided an environmental risk assessment phase I and II according to the guideline for environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00, corr2).

Table 7: Summary of main study results

Substance (INN/Invented Name): Lasmiditan succinate			
CAS-number (if available):439239-92-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Kow (pH 4) = -0.561 log Kow (pH 7) = 0.978 log Kow (pH 9) = 2.77	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.77	not B
	BCF		B/not B
Persistence	DT50	472	vP
Toxicity	CMR	Category 2 Reproductive Hazard (H361d)	T
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default	1	µg/L	> 0.01 threshold Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106 or …	*Koc* $_{loamy\ sand}$=28595 ml g^{-1} *Koc* $_{clay\ loam}$=14280 ml g^{-1} *Koc* $_{sandy\ loam}$=14397 ml g^{-1} *Koc* $_{sludge}$ = 234 ml g^{-1} *Koc* $_{sludge}$ = 81.1 ml g^{-1}	terrestrial studies not triggered
Transformation in sewage sludge	OECD 314B /302B	K_{STP} = 0.0491 d^{-1} DT50 = 14 d % mineralisation = 0.3	Main TP: 2,4,6-trifluoro-N-{6-[(S)-hydroxy(methylpiperidin-4-yl)methyl]pyridine-2-yl}benzamid
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Taunton River / Weweantic River $DT_{50,\ 20\ °C,\ water}$ = 6.23 / 3.78 d $DT_{50,\ 20\ °C,\ sediment}$ = 350 / 154 d $DT_{50,\ 20\ °C,\ whole\ system}$ = 222 / 148 d % shifting to sediment = 82 / 74.5 (day 14) % Non-extractables = 27.5 / 35.3 % mineralisation = 0.124 / 0.294	vP in both systems

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Raphidoceis subcapitata*	OECD 201	NOEC	1500	µg/L	
Daphnia magna Reproduction Test	OECD 211	NOEC	2700	µg/L	
Daphnia magna, Acute Immobilisation Test, 48 h	OECD 202	EC50	17000	µg/L	Additional test, not required
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	5200	µg/L	
Fish, Acute Toxicity Test / *Pimephales promelas,* 96h	OECD 203	LC50	72000	µg/L	Additional test, not required
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	10000	µg/L	Total respiration rate
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	86 430	mg/ kg	2% organic carbon normalized 10% o.c, *Chironomus riparius*

2.4.6. Discussion on non-clinical aspects

Lasmiditan is claimed to be a high-affinity, highly selective 5-HT_{1F} receptor agonist. According to receptor-binding data obtained in studies CNS571 and CLP-005c, the K_i of lasmiditan for the cloned human 5-HT_{1F}-receptor amounts to 2.2 and 1.8 nmol/l, respectively. In addition, lasmiditan was found to activate cloned human 5-HT_{1F} receptors with an EC_{50} of 3.74 nmol/l (Study CLP-005c). Therefore, maximal binding to and activation of 5-HT_{1F} receptors can be expected to occur with low-nanomolar concentrations of lasmiditan.

However, clinical effective doses of lasmiditan are associated with much higher plasma concentrations. At a dose of 200 mg lasmiditan, the total plasma C_{max} of lasmiditan amounts to 260 ng/ml, corresponding to a concentration of 689 nmol/l (the unbound fraction amounts to 117 ng/ml or 310 nmol/l), which is more than 100-times higher than the K_i-values derived from the binding studies.

Therefore, the Applicant was asked to critically discuss the hypothesis that clinical efficacy of lasmiditan in acute treatment of migraine is solely related to an activation of 5-HT_{1F} receptors, taking into account the above-mentioned data.

In his response document, the Applicant provided the following arguments:

- The unbound concentrations of lasmiditan at efficacious doses are not high enough to activate other receptors.
- Clinically efficacious doses of triptans have ratios of unbound plasma concentration to 5-HT_{1B} K_i that are similar to those for lasmiditan at the 5-HT_{1F} receptor.
- It is not precisely known if the clinical effects of lasmiditan are mediated via receptors in the periphery, central CNS, or both. As such, the unbound levels in the brain could be approximately three times lower based on a preclinical rodent study (Study NS22).
- The expectation of the unbound exposure to K_i ratio approximating unity is not achieved for many clinically efficacious compounds and is not, as such, a reason to doubt the pharmacological mechanism of action for lasmiditan.

However, since:

- The data presented for the triptans sumatriptan, eletriptan and naratripan suggest that for 5-HT_{1F}-receptor agonists, unbound concentrations about 5- to 6-fold higher than the Ki-value at the 5-HT_{1F}-receptor are clinically active and that the ratios of 25.4, 62.7 and 168 observed for clinical lasmiditan doses of 50, 100 and 200 mg at the 5-HT_{1F}-receptor, clearly exceed this range.
- According to a publication by Jansson-Lofmark et al. (2020), a ratio of unbound plasma exposure/*in vitro* potency of >100 (as found for the 200 mg lasmiditan dose with a ratio of 168 for the 5-HT_{1F}-receptor) was only observed for less than 4% of the investigated 164 drugs.

The CHMP concluded that the possibility that, in addition to an activation of 5-HT_{1F} receptors, an additional, currently uncharacterized mechanism of action contributes to the clinical efficacy of lasmiditan in the acute treatment of migraine, can currently not be excluded. Respective information is included in SmPC section 5.1.

● Trigeminal nerve activation has been implicated in pathogenesis of human migraine disease. Efficacy of lasmiditan was demonstrated in different rat and mouse models of trigeminal nerve activation, that are considered to reflect aspects of human migraine disease. However, the doses of lasmiditan that were effective in these models, varied strongly. With regard to the observed large differences in effective lasmiditan doses, the Applicant was asked to discuss the predictivity of the used animal models for the clinical use of lasmiditan in the acute therapy of migraine.

In his response, the Applicant concluded that, due to the fact that experimental design variables had the ability to dramatically change the potency observed of lasmiditan, these preclinical models were not considered suitable to reliably predict efficacious clinical doses, but rather to provide evidence for the principal ability of lasmiditan to inhibit trigeminal nerve activation as a potential antimigraine mechanism of action. This has been accepted by CHMP

● Repeated administration of lasmiditan promoted transient cephalic and hindpaw allodynia that could be reinstated with stress or nitric oxide donor. This model has been suggested as a preclinical model of Medication Overuse Headache (MOH) (De Felice et al. 2010). However, the predictive validity of this preclinical model is not fully established, and it is agreed that the propensity of lasmiditan to induce MOH must ultimately be assessed clinically.

Concerning effects on the tone of blood vessels, the lack of vasoconstricitve effects of lasmiditan on a spectrum of animal and human blood vessels clearly differentiates lasmiditan from the triptan class of compounds presently used for the acute treatment of migraine attacks.

Lasmiditan was evaluated for broad behavioural and CNS properties through a series of pharmacological tests in male CD-1 mice, in which sensorimotor reactivity to an auditory stimulus was significantly increased for all doses of lasmiditan evaluated. The Applicant was asked to discuss the potential clinical relevance of this effect, in the context of an acute treatment of migraine attacks.

In their response, the Applicant pointed out that the increase in sensorimotor reactivity to an auditory stimulus in mice was in contrast to reductions in a number of other CNS activities.

With respect to data from clinical trials that actually demonstrate significantly decreased proportions of patients experiencing phonophobia during migraine attacks treated with lasmiditan, it can be concluded that the finding in mice are not relevant to humans at clinically relevant doses of lasmiditan

In the 13- and 26-week studies, lasmiditan was also associated with exacerbation of the age-related spontaneously occurring condition, chronic progressive nephropathy (CPN). However, the exacerbation of CPN was not considered of direct human relevance due to a species-specific, spontaneous age-related background nature of this finding.

Based on findings indicative of adverse renal toxicity (medulla tubulointerstitial nephropathy), the lowest NOAEL of 30 mg/kg ($AUC_{0\text{-}24hr}$ 11450 ng•hr/mL) was observed in male rats in the 13-week study. A review of clinical trial data did not show evidence of an adverse effect of lasmiditan on renal function. It has been clarified that, based on the exposure multiple relative to the human therapeutic exposure and the lack of signals associated with renal effects in the clinical development program, the risk of renal toxicity at clinically relevant exposures is low.

Heart: An exacerbation of cardiomyopathy, a spontaneously occurring change in aging rats was noted in the 26-week rat study. In this study, degenerative cardiomyopathy was evident in controls and lasmiditan-treated animals, with increased severity in males given 200 mg/kg and increased incidence and severity in females given ≥100 mg/kg (8202968. These changes in the heart were interpreted by the Applicant as test article-related exacerbations of a species-specific spontaneously-occurring background condition (Berridge et al. 2016; Chanut et al. 2013; Jokinen et al. 2011).

Pharmacokinetic investigations have shown that lasmiditan distributes in the heart, where 5-HT_{1F} receptors are expressed. The Applicant was asked to clarify if a pharmacological effect at 5-HT_{1F} receptors could have contributed to the degenerative cardiomyopathy in rats observed in chronic toxicity studies. CHMP has agreed that the exacerbation of cardiomyopathy, which occurred at exposures greater than 20-fold higher than human exposure at the maximum 200-mg dose, was not of direct human relevance, assuming a species-specific, spontaneous age-related background nature of this finding.

In Study DV0302, the cardiovascular effects of a 20-minute IV infusion of lasmiditan hemisuccinate (0. 0.6, 2 and 6 mg/kg) on left ventricular function, systemic blood pressures, and electrocardiograms in conscious beagles dogs were tested. No compound-related changes in systemic arterial pressures, left ventricular inotropic state, or electrocardiograms occurred at any time point throughout the study. The highest dose of 6 mg/kg was considered a NOAEL. Based on this study it could be concluded that Lasmiditan involves no drug-related findings on the cardiovascular system. However, increases in QTc interval and QRS duration were observed in a 39-week repeat dose dog toxicity study (N° 8204494) at doses above 40 mg/kg with a trend from 30 mg/kg. In addition, in the human PK/PD ICH E14 TQT study, the results suggest a significant effect of lasmiditan on cardiac repolarization in terms of prolongation in the subgroup of female volunteers. Pharmacokinetic investigations have shown that lasmiditan distributes in the heart, where 5-HT_{1F} receptors are expressed. The applicant was asked to clarify if a pharmacological effect at 5-HT_{1F} receptors could have contributed to the effects on QTc interval and QRS duration.
In their response, the Applicant pointed out that increases in QRS, QT, and QTc intervals were reported at a high dose (Cmax >10-fold higher than that in humans at 200 mg). The modest effect on QT and QTc was observed at mean plasma Cmax values between 2664 ng/mL and 4265 ng/mL. Based on a 40% to 55% protein binding, the free plasma concentrations observed and associated QT/QTc prolongation align well within the expected hERG inhibition concentration response curve (IC_{50} 1170 ng/mL). It is therefore unlikely that 5-HT1F agonism contributed to any ECG effects on study given that lasmiditan has a target affinity (Ki) of 0.84 ng/mL which is more than 1000-fold lower than the free plasma concentrations where the ECG effects were observed.

In addition, the lack of contribution of Lasmiditan activation of 5HT1F receptors in the heart to the functional cardiac effects in the dog is further supported by the fact that expression of this receptor in cardiomyocytes or blood vessels of the heart is reported to be low or absent (Human Protein Atlas [WWW]; Bouchelet et al. 2000; Vila-Pueyo 2018).

Carcinogenicity

For the 2-year rat carcinogenicity study, the Applicant provided on request a listing, containing for each observed unscheduled death in the study information concerning gender of the animal, treatment group,

study day at which death occurred, possible underlying reason for death (if known) and estimated cumulative life-time exposure (AUC) to lasmiditan until day of death. On basis of the data provided by the Applicant, the following picture emerged: Unscheduled deaths occurred earlier in male animals treated with the lasmiditan doses of 10, 20 and 75 mg/day than in the respective untreated control group (reflected by a left-shift in the Kaplan-Meier survival curves). A subgroup analysis revealed that in particular unscheduled deaths due to pituitary neoplasia occurred earlier in the lasmiditan-treated male animals than in the male control group. The relevance of these findings in terms of human risk is unknown and this has been addressed in SmPC section 5.3.

Concerning the 26-Weeks carcinogenicity study in transgenic rasH2 mice, the applicant was expected to clarify its position regarding the higher incidence of bronchiolo-alveolar carcinoma observed at the high dose in females based on values reported by Paranjpe et al., 2013 and Nambiar et al., 2012 and the fact that no bronchiolo-alveolar carcinoma was observed in the positive group control.

In his response, the applicant presented more or less the same data which were submitted in the dossier. Based on Madhav G Paranjpe *et.al* (*Int J Toxicol*. Jan-Feb 2013; 32(1):48-57), the combined incidence of 16% observed in females (HD group) is above the 7.74% average value reported. Moreover, a BAC value of 12% is also above the value reported by Nambiar *et al* (2012): lung bronchiolo-alveolar adenocarcinomas (mean 1.4-2.4%; range 0-5%). Nevertheless, it is agreed that no treatment-related increase in BA tumors was observed in either male or female rats treated for two years, and no other pre-neoplastic proliferative or non-neoplastic pulmonary changes.

Reproductive and developmental toxicity

A low incidence of fetal cardiovascular (ventrical septal) defects were observed in the high dose group of the rabbit dosed orally in one of the conducted EFD studies. Although similar findings were not observed in other EFD studies conducted in that species (second oral EFD study, IV EFD study), a lasmiditan relationship cannot be excluded. In addition, one rabbit fetus was reported with meningocele and corresponding absent skull bones at the high dose level of 115 mg/kg/day. Although it is acknowledged that drug-related toxicity was observed in the dam producing this litter and in the litter, this rare malformation is not reported in the historical database and hence a relationship to treatment cannot be excluded. The Applicant was asked to discuss this point.

The Applicant provided an updated historical control database reporting occurrence of cranial meningocele in the 0%-5% range (based on litter incidence). Since this malformation was reported in one isolated high dosed fetus from a doe with significant toxicity and considering that the underlying skull malformations were within HC range, it can be concluded that a treatment-relationship appears as unlikely.

In the pre- and post-natal development study, treatment-related decreases in mean numbers of implantation sites in F1 offspring were reported in the reproductive phase and led to reduced numbers of delivered pups and live pups per litter. Findings in the pre-postnatal development study in F1 offspring occurred at the highest dose with exposure margins towards the human therapeutic exposure of 50. Therefore, these findings do not have to be reflected in the SmPC.

Other toxicity studies - Immunotoxicity

According to Guideline ICH S8 "Immunotoxicity studies for human pharmaceuticals", all new human pharmaceuticals should be evaluated for the potential to produce immunotoxicity. A weight of evidence review should be performed, based on information from all available studies to determine whether a cause for concern exists. No such data had been initially submitted by the Applicant.

On request, the Applicant has provided a thorough weight of evidence review in accordance with ICH S8. Factors that were considered included findings from the standard toxicology studies, pharmacological properties of lasmiditan, intended patient population, structural similarities to known immunomodulators, disposition of lasmiditan and information from clinical trials with lasmiditan. As a specific cause for concern was not identified, additional immunotoxicity studies are not considered necessary.

Other toxicity studies - Phototoxicity

The molar extinction coefficient (MEC) of lasmiditan was greater than the threshold (1000 Lmol-1/cm) at the maximum absorption peaks at 224, 255, 298 nm. To further investigate the phototoxic potential of lasmiditan, a 3T3 NRU-PT study was conducted and deemed negative. As it was not completely clear if the study was conducted at standard settings (UVA filter >320 nm) or if modified irradiation settings were included to better fit the absorption spectra of lasmiditan in the lower range of the UV visible spectrum, the applicant was asked to provide information on which filter was used in the 3T3 NRU-PT study and justify the chosen filter.

The applicant provided information on the filter used in the 3T3 NRU-PT assay as requested. The assay was conducted according to the current guideline "ICH Guidance S10 on photosafety evaluation of pharmaceuticals" (EMA/CHMP/ICH/752211/2012)" for systemically applied medicines. The study was conducted at standard settings (UVA filter >320 nm) to filter out most UV-B, which is highly cytotoxic and would confound interpretation of the assay. Despite the facts that the maximum absorption peaks for lasmiditan were determined at 224, 255 and 298 nm (all UVB with MEC > 1000 $Lmol^{-1}$/cm) and had affinity to melanin containing tissues (eye, skin) no further phototoxicity testing will be necessary. Lasmiditan is photostable and to date no case of phototoxicity was detected under clinical settings.

No risks were identified for organisms in surface water, in groundwater, in the sediment compartment and for microorganisms. A risk assessment for the terrestrial compartment was not required due to the low binding affinity of the active substance lasmiditan to sewage sludge. A bioaccumulation potential is not indicated based on the logKow <3 and A PBT assessment is not required. However, the active substance can be classified as very persistent (vP) in sediments based on DT50 values of >180 days, determined in a study on transformation in water/sediment systems. Lasmiditan meets the criterion for toxic (T) since it is classified as a Category 2 Reproductive Hazard (CLP Hazard Statement Code H361d). Therefore, the substance is very persistent and toxic but not considered a PBT or vPvB substance. Main transformation products >10% were not detected. However, metabolism data and a transformation study in sewage sludge shows the formation of one main metabolite.

2.4.7. Conclusion on the non-clinical aspects

Based on the data provided, it can be expected that lasmiditan will not pose a risk to the environment when used in accordance with the SmPC.

In general, the submitted non-clinical data package is considered sufficient to support marketing authorisation.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

The following studies have been conducted to characterise PK of lasmiditan.

Mass balance

Phase 1 Mass balance Study LAHH investigated the Absorption, Metabolism, and Excretion of [14C]-Lasmiditan Following Single Oral Dose Administration in Healthy Male and Female Subjects

Five metabolites, M8, [S,R]-M18, M7, [S,S]-M18, and M3, were quantified in plasma via LC-MS/MS and accounted for 47.5%, 10.5%, 7.7%, 2.1%, and 0.5% of total plasma radioactivity, respectively.

Maximal levels of total radioactivity in plasma and whole blood were reached with a median tmax of 2.52 hours (range: 2.00 to 4.00 hours) and 3.00 hours (range: 2.00 to 5.03 hours), respectively.

Levels of total radioactivity in plasma and whole blood were quantifiable up to 24 hours post-dose in all 8 subjects, up to 36 hours for 3 of the 8 subjects for plasma radioactivity and 5 of the 8 subjects for whole blood radioactivity, and up to 48 hours for 1 subject for both plasma and whole blood total radioactivity.

The mean recovery of total radioactivity in urine and faeces was 95% over the 312-hour collection period with recovery in individual subjects ranging from 86% to 101%.

The primary route of excretion of the total radioactivity was in the urine; high recovery (86.8%) of drug-related material in urine indicated that lasmiditan was well absorbed.

Urinary excretion of lasmiditan was minimal, accounting for 2.91% of the administered dose.

Metabolite M8 (S-enantiomer only) represented approximately 66% of the dose in urine; 14 additional metabolites were identified in urine, each accounting for ≤5% of the dose.

Lasmiditan was detected in faeces from only 1 subject at a trace level (<1% of the dose) and the 3 faecal metabolites including S-M8 represented ≤3% of the dose.

None of the identified metabolites for lasmiditan are pharmacologically active.

BA of 200 mg lasmiditan under fed and fasted conditions

Food study 104-LAHR was a randomized open-label study to compare the BA of Lasmiditan 200 mg under Fed and Fasted Conditions in Healthy Male and Female Subjects

Figure 3: Lasmiditan arithmetic mean (±SEM) plasma concentration-time profiles following single oral administrations of lasmiditan 200 mg in both fed and fasted conditions in healthy subjects (linear representation) (N=30)

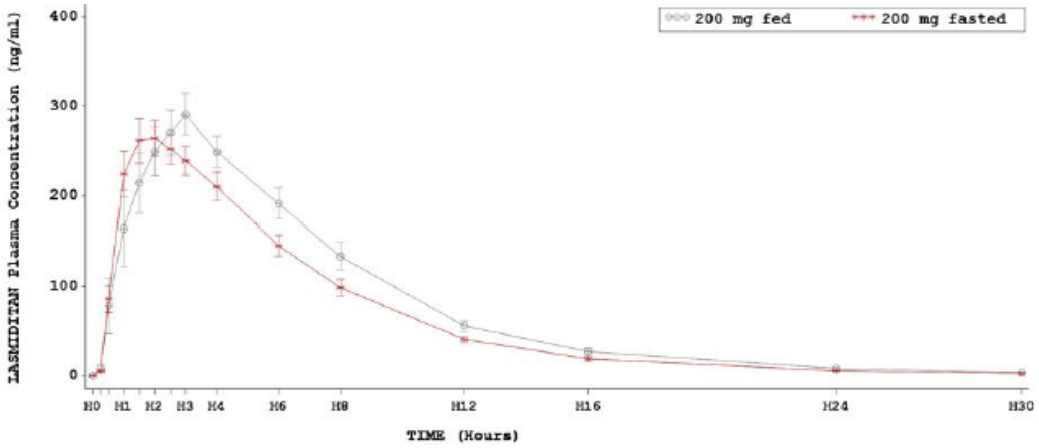


Table 8: ANOVA results for food effect analysis following a single oral dose of lasmiditan 200 mg in the fed and the fasted condition in healthy subjects (N=30)

Parameter (unit)	Test (200 mg fed) (a)	Reference (200 mg fasted) (a)	Test / Reference (b)
C_{max} (ng/mL)	365.1 [323.1 - 412.5]	300.2 [265.7 - 339.2]	**1.216** [1.052 -1.405]
AUC_{0-t} (ng.h/mL)	2097.9 [1876.7 - 2345.2]	1769.5 [1582.9 - 1978.1]	**1.186** [1.099 - 1.278]
AUC_{0-inf} (ng.h/mL)	2116.5 [1893.4 - 2365.9]	1782.9 [1594.9 - 1992.9]	**1.187** [1.102 - 1.279]

C_{max}: Maximum observed plasma concentration AUC_{0-t}: Area under the plasma concentration versus time curve from time 0 to the time t of the last quantifiable concentration, AUC_{0-inf}: Area under the plasma concentration versus time curve from time 0 to infinity
(a) Geometric lsmean (90% confidence interval)
(b) Point estimate (90% confidence interval) for the Test / Reference geometric lsmean ratio derived from ANOVA
90% reference confidence interval [0.80; 1.25]
Source: Section 14.2.1.2.3

Food intake resulted in a minor effect on Cmax and AUC0-inf of lasmiditan, as reflected by a ratio (lasmiditan under fed condition/fasted condition) of 1.216 for Cmax (90% CI: 1.052-1.405) and of 1.187 for AUC0-inf (90% CI: 1.102-1.279).

A post-hoc analysis suggested a possible effect of gender on lasmiditan main PK parameters (Cmax and AUC0-inf). An increase of approximately 20-30% in Cmax and 30% in AUC was noted in female subjects compared to male subjects. This indicated that gender had an effect on the PK of lasmiditan with higher Cmax (~20-30%) and AUC (~30%) in women compared to men, whether lasmiditan was administered in fed or fasted conditions.

Dose proportionality

Lasmiditan PK data after oral dosing in healthy subjects were evaluated in several studies with multiple dose levels (Studies 102/LAHS, 103/LAHQ, 105/LAHP, LAHB) and pooled together in an analysis to evaluate dose proportionality over a dose range from 25 to 400 mg. Over this dose range, the geometric mean values for lasmiditan Cmax and AUC(0-∞) increased in a manner that was greater than dose proportional.

Table 9: Dose-Proportionality Analysis Following Oral Administration of Lasmiditan

Analyte	Dose Range (mg)	PK Parameter		Ratio of Dose Normalized Geometric Means (90% CI)		Increase per doubling the dose	CVw(%)	CVb(%)	DP Ratio
LY573144	25-400	AUC(0-inf)	(ng*hr/mL)	1.36	(1.29, 1.43)	2.16(2.13,2.19)	15.0	36.2	5.7
	25-400	Cmax	(ng/mL)	1.59	(1.46, 1.72)	2.24(2.20,2.29)	24.1	36.6	3.1
	50-200	AUC(0-inf)	(ng*hr/mL)	1.20	(1.13, 1.28)	2.19(2.12,2.26)	15.1	37.9	3.5
	50-200	Cmax	(ng/mL)	1.34	(1.22, 1.47)	2.31(2.21,2.42)	22.9	36.7	2.2

Abbreviations: AUC(0-inf) = area under the concentration versus time curve from zero to infinity; CI = confidence interval; Cmax = maximum observed drug concentration; CVw = within subject variability coefficient of variation; CVb = between subject variability coefficient of variation; PK = pharmacokinetic; DP = dose proportionality
DP Ratio is the maximal fold up-to which dose proportionality is achieved by the criteria of 90% CI of ratio of dose normalised geometric means lies completely inside the reference interval of (0.80, 1.25).
Model: log(PK) = log(Dose)

Over a clinical dose range of 50 to 200 mg, Cmax and AUC(0-∞) increased by 4.8- and 5.4-fold, respectively, with a 4-fold increase in dose. While neither dose proportionality nor non-dose proportionality could be strictly concluded as the 90% CI for Rdnm values spanned across the limits of 0.8 to 1.25, the increase in exposure beyond dose proportionality was within the range of the estimated interindividual PK variability (%CV ~ 37%). Lasmiditan exposure increased in a dose-dependent manner that was considered to be approximately linear with dose over a clinical dose range of 50 to 200 mg.

Time dependency – Drug-Drug Interaction

Multiple-ascending dose study LAHE aimed to evaluate the safety, tolerability, PK, and potential withdrawal symptoms following once-daily dosing of lasmiditan at 200 mg (Cohort 1) and 400 mg (Cohort 2) dose levels.

Cohort 1

Cohort 1 of the study aimed to examine the effect of multiple doses of lasmiditan upon CYP1A2, CYP2C9, and CYP3A activity via concomitant administration and PK monitoring of a probe drug cocktail including caffeine (CYP1A2 substrate), tolbutamide (CYP2C9 substrate), and midazolam (CYP3A4/5 substrate).

Single dose of drug cocktail on Days -3 and 7; once-daily dosing of lasmiditan (200 mg/day, given orally, as 1 x 200-mg film-coated tablet) or placebo (at a ratio of 7:3 lasmiditan to placebo) on Days 1 to 7.

On Days -3 and 7, subjects were administered a drug cocktail, consisting of 100-mg oral dose of caffeine (as caffeine base) in tablet form, 500-mg oral dose of tolbutamide in tablet form, and 2-mg dose of midazolam oral syrup, administered concurrently with the lasmiditan dose.

Cohort 2

Lasmiditan 400 mg/day, given orally, once-daily as 2 x 200-mg film-coated tablet on Days 1-7

Figure 4: Arithmetic Mean (one sided SD) Plasma concentration profiles of lasmiditan for Study LAHE

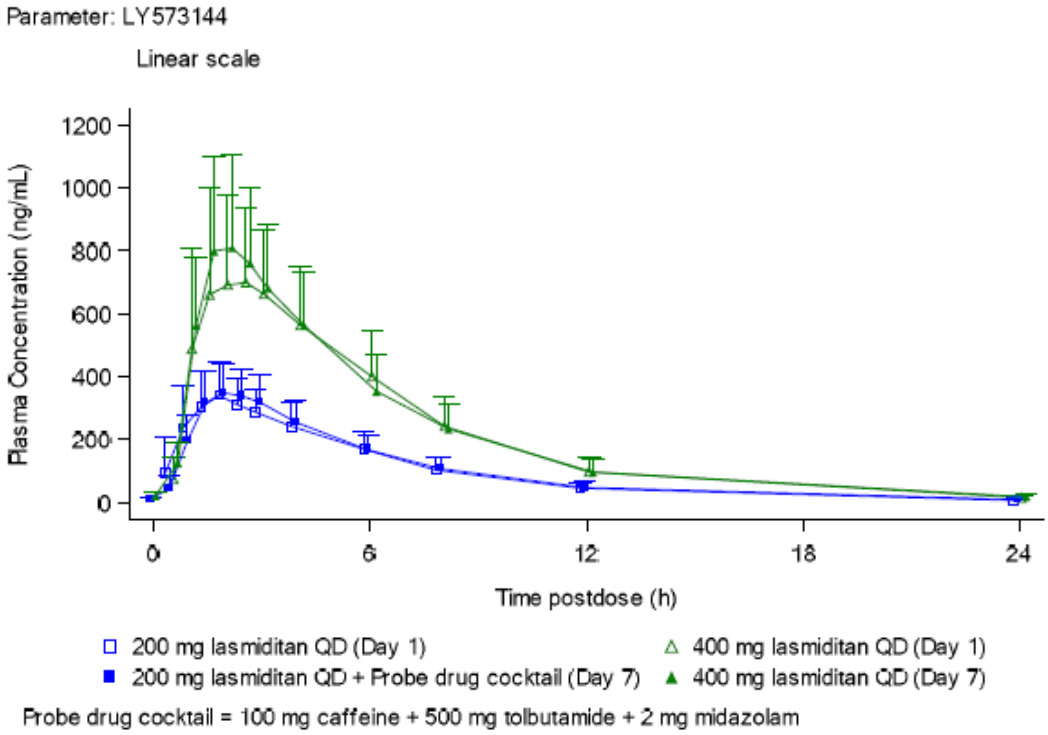


Table 10: Summary of Pharmacokinetic Parameters of Lasmiditan (LY573144) on Days 1 and 7 Following Single and Repeated Oral Daily Dosing of 200 and 400 mg Lasmiditan

Analyte: LY573144

	Geometric mean (Geometric CV%)							
Parameter	200 mg lasmiditan QD (Day 1) (N=28)	n	200 mg lasmiditan QD + Probe drug cocktail (Day 7) (N=27)	n	400 mg lasmiditan QD (Day 1) (N=15)	n	400 mg lasmiditan QD (Day 7) (N=14)	n
Cmax (ng/mL)	349 (32%)	28	353 (29%)	26	750 (44%)	15	808 (41%)	14
tmax (h)#	2.00 (0.50-4.00)	28	2.00 (1.50-3.02)	26	2.00 (1.00-4.00)	15	2.00 (1.50-2.50)	14
AUC(0-∞) (ng.h/mL)	2110 (32%)	28			4600 (40%)	15		
%AUC(tlast-∞) (%)	1.73 (45%)	28			1.39 (41%)	15		
AUCτ (ng.h/mL)	2070 (32%)	28	2160 (29%)	26	4530 (39%)	15	4690 (36%)	14
t½ (h)~	4.13 (3.46-5.14)	28	4.34 (3.58-5.34)	26	3.82 (3.19-4.43)	15	4.05 (3.45-5.18)	14
CL/F (L/h)	94.8 (32%)	28	92.8 (29%)	26	87.0 (40%)	15	85.4 (36%)	14
Vz/F (L)	564 (32%)	28	581 (27%)	26	479 (37%)	15	498 (38%)	14
RA_AUC	NA		1.03 (18%)	26	NA		1.02 (13%)	14
RA_Cmax	NA		1.02 (21%)	26	NA		1.06 (19%)	14
RI	NA		1.01 (18%)	26	NA		1.00 (13%)	14

Probe drug cocktail = 100 mg caffeine + 500 mg tolbutamide + 2 mg midazolam
Abbreviations: %AUC(tlast-∞) = percentage of AUC(0-∞) extrapolated; AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUCτ = area under the concentration versus time curve during one dosing interval; Cmax = maximum observed drug concentration; CL/F = apparent total body clearance of drug calculated after extra-vascular administration; N = number of subjects; n = number of observations; RA_AUC = Accumulation ratio based upon AUCτ; RA_Cmax = Accumulation ratio based upon Cmax; RI = the linearity ratio between AUCτ on Day 7 and Day 1 AUC(0-∞); tmax = time of maximum observed drug concentration; t½ = half-life associated with the terminal rate constant in non-compartmental analysis;
Vz/F = apparent volume of distribution during the terminal phase after extra-vascular administration; NA = Not applicable
Median (range)
~ Geometric mean (range)

Following daily dosing, lasmiditan reached a median tmax of 2 hours post-dose on Day 1 and 7. After reaching Cmax, plasma concentrations of lasmiditan declined in a monophasic manner, with a geometric mean t1/2 of approximately 4 hours for both 200- and 400-mg lasmiditan dose levels on Days 1 and 7.

Steady-state for lasmiditan appeared to be reached by the end of Day 2 for both 200- and 400-mg dose levels. No accumulation of lasmiditan was observed with repeated daily dosing. The ratio of AUC(0-τ) at steady state to AUC(0-∞) after a single dose was approximately 1. Therefore, lasmiditan PK is not expected to change with time with chronic dosing. Geometric mean values for lasmiditan AUCτ and Cmax appeared to increase in a manner that was approximately dose-proportional between 200- and 400-mg doses of lasmiditan alone.

Following repeated daily dosing of 200 mg lasmiditan, changes in geometric mean Cmax and AUC parameters for co-administration with caffeine, tolbutamide and midazolam were all less than 12% relative to a single dose of 200 mg lasmiditan. The 90% CI for the ratio of LS means for all parameters were within 0.8 to 1.25.

Pharmacokinetics in target population

Study LAHC was conducted to evaluate the PK of Lasmiditan in migraineurs during acute migraine attacks and during Inter-Ictal Periods under open-label conditions.

Acute migraine attacks are frequently accompanied by some gastrointestinal symptoms, such as nausea and vomiting. Gastric motility studies also indicated that many migraine patients developed gastroparesis during acute migraine attacks. Changes in gastric motility may lead to changes in the pharmacokinetics (PK) of drugs for migraine abortive treatment, which may reduce the effectiveness of migraine treatment. The goal of this study is to assess the PK of lasmiditan in migraineurs during acute migraine attacks and during inter-ictal periods.

Table 11: Statistical Analysis of the Pharmacokinetic Parameter Estimates of Lasmiditan Following Single Dosing of 200 mg Lasmiditan during a Migraine Attack (Period 1) and during the Inter-Ictal Period (Period 2)

Analyte: LY573144

Parameter	Treatment	N	Geometric least squares means	Ratio of geometric least squares means Test : Reference	90% CI for the ratio (Lower, Upper)
Cmax (ng/mL)	200 mg lasmiditan (Period 1) (Reference)	16	233		
	200 mg lasmiditan (Period 2) (Test)	16	227	0.976	(0.863, 1.10)
AUC(0-tlast) (ng.h/mL)	200 mg lasmiditan (Period 1) (Reference)	16	1545		
	200 mg lasmiditan (Period 2) (Test)	16	1591	1.03	(0.915, 1.16)
AUC(0-∞) (ng.h/mL)	200 mg lasmiditan (Period 1) (Reference)	13	1513		
	200 mg lasmiditan (Period 2) (Test)	14	1656	1.09	(0.994, 1.21)

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; CI = confidence interval; Cmax = maximum observed drug concentration; N = number of subjects
Period 1 - Acute migraine attack; Period 2 - Inter-ictal period
Model: Log(PK) = PERIOD + SUBJECT + RANDOM ERROR, where SUBJECT is fitted as a random effect

The geometric mean Cmax, AUC(0-tlast), and AUC(0-∞) values for the inter-ictal period (Period 2) for lasmiditan were similar to values obtained during the migraine attack (Period 1), with the 90% CIs for the ratios of geometric LS means containing unity and falling completely within the bioequivalence limits (0.8 to 1.25) for all 3 parameters. The time to maximum plasma concentration was similar (tmax: during acute attacks 1.77 hours, inter-ictal period 2.08 hours).

Renal impairment

Renal impairment study LAHN examined the PK of a single dose of 200 mg lasmiditan in subjects with normal and impaired renal function following an open-label, parallel-group adaptive design.

The study planned for the enrolment of up to 32 subjects using an adaptive design that could have included up to 3 groups of subjects with different degrees of renal impairment and one group of 8 control subjects with normal renal function.

Male and female adult subjects were to be categorized by mild, moderate, severe renal impairment or healthy renal function according to the definition of the National Kidney Foundation and using the Modification of Diet in Renal Disease (MDRD) classification. Eight subjects with severe renal impairment (eGFR < 30 mL/min/1.73 m2) were enrolled first (Group 2).

Adaptive Group 3 (Moderate Renal Impairment) and Group 4 (Mild Renal Impairment) were to be enrolled, following the review of safety and PK data from subjects with severe renal impairment (Group 2) by the investigator.

Table 12: Summary of Statistical Analysis of Pharmacokinetic Parameters for Lasmiditan - ANOVA

Parameters	Group	Geometric LS Mean[a]	Comparison	Adjusted p-value	Ratio (%)	90% Confidence Limits (%)	
						Lower	Upper
C_{max}	Normal (n=8)	259	Severe vs Normal	0.5343	112.97	80.64	158.26
	Severe (n=8)	293					
$AUC_{(0\text{-}tlast)}$	Normal (n=8)	1580	Severe vs Normal	0.3948	117.76	84.84	163.45
	Severe (n=8)	1870					
$AUC_{(0\text{-}\infty)}$	Normal (n=8)	1600	Severe vs Normal	0.3872	118.08	85.07	163.90
	Severe (n=8)	1890					

[a] C_{max} is presented in ng/mL, $AUC_{(0\text{-}tlast)}$ and $AUC_{(0\text{-}\infty)}$ are presented in ng·h/mL

Lasmiditan

Following single dose oral administration of one 200-mg lasmiditan tablet, maximal lasmiditan plasma concentrations were reached with a median (range) Tmax of 2.50 h (1.00-3.00 h) in subjects with normal renal function and a median Tmax of 1.78 h (0.75-3.00 h) in subjects with severe renal impairment. Plasma concentrations declined thereafter in a log-linear manner with a mean terminal elimination half-life of approximately 4 h in both groups.

The ratio of geometric LS means are 112.97% [80.64-158.26], 117.76% [84.84-163.45], and 118.08% [85.07-163.90] for Cmax, AUC(0-tlast) and AUC(0-∞), respectively. Hence, the 90% CIs for the ratio of geometric LS means did not fulfil BE criteria, however, included unity suggesting similar lasmiditan peak and systemic exposure between subjects with severe renal impairment as compared to healthy controls.

M8 Metabolite

Following single dose oral administration of one 200-mg lasmiditan tablet, maximal (S)-M8 plasma concentrations were observed at a median time of 2.50 h and 2.88 h for subjects with normal renal function and subjects with severe renal impairment, respectively. Plasma concentrations declined thereafter in a log-linear manner with a mean terminal elimination half-life of approximately 13 h and 29 h in subjects with normal renal function and subjects with severe renal impairment.

An ANOVA analysis was conducted yielding ratios of geometric LS means of 115.81% [87.53-153.24], 171.36% 131.94-222.55], and 249.81% [200.03-311.97] for Cmax, AUC(0-tlast) and AUC(0-∞), respectively. Only the corresponding 90% CI for Cmax included unity suggesting an increase in (S)-M8 systemic exposure in subjects with severe renal impairment in comparison to subjects with normal renal function.

Hepatic impairment

Hepatic impairment study LAHF examined the PK of a Single Dose Study of 200 mg lasmiditan in subjects with normal and impaired hepatic function (mild, moderate) following an open-label, parallel-group design.

Table 13: Summary of Statistical Analysis of PK Parameters for Lasmiditan in Subjects with Varying Degrees of Hepatic Impairment After a Single 200-mg Oral Dose Lasmiditan - ANOVA

Parameters	Group	Geometric LSmeans[a]	Comparison	Adjusted p-value	Ratio (%)	Adjusted 90% Confidence Limits (%)	
						Lower	Upper
C_{max}	Normal (n=8)	220	Mild vs Moderate	0.8669	88.85	53.77	146.82
	Mild (n=8)	261	Mild vs Normal	0.6478	118.59	78.53	179.07
	Moderate (n=8)	294	Moderate vs Normal	0.2704	133.47	90.08	197.76
$AUC_{(0\text{-tlast})}$	Normal (n=8)	1590	Mild vs Moderate	0.7354	84.02	50.86	138.80
	Mild (n=8)	1750	Mild vs Normal	0.8254	110.47	76.73	159.07
	Moderate (n=8)	2080	Moderate vs Normal	0.4402	131.48	81.64	211.77
$AUC_{(0\text{-}\infty)}$	Normal (n=8)	1610	Mild vs Moderate	0.6946	82.63	49.90	136.84
	Mild (n=8)	1790	Mild vs Normal	0.7919	111.46	77.78	159.72
	Moderate (n=8)	2170	Moderate vs Normal	0.3783	134.89	83.73	217.32

[a] C_{max} is presented in ng/mL, $AUC_{(0\text{-tlast})}$ and $AUC_{(0\text{-}\infty)}$ are presented in ng·h/mL

Source: Appendix 16.1.9.2

There were about 18-33% increases in Cmax and increases in AUC of about 10-35% in AUC in patients with mild resp. moderate hepatic impairment relative to healthy controls. The time to maximum plasma concentrations shortens with increasing degree of renal impairment (Tmax: control 2.5 hr, mild impairment 2.0 hr, moderate impairment 1.4 hr). Inversely, the elimination half live (t1/2) increases

with increasing degree of hepatic impairment (t1/2: control 5.1 hr, mild impairment 5.7 hr, moderate impairment 7.8 hr).

PK in the elderly

Study LAHA examined the effect of age on the pharmacokinetics, safety, and tolerability of lasmiditan in healthy subjects.

This was a SD study to determine the PK of lasmiditan following a single 200 mg oral dose in healthy elderly and young subjects. Two groups of subjects were evaluated as follows:

- Group 1 (healthy elderly subjects; ≥65 years): 200 mg lasmiditan and placebo in a randomized, double-blind, 2-period crossover design.
- Group 2 (healthy young subjects; 18 to 45 years, inclusive): 200 mg lasmiditan in an open-label design.

Subjects in Group 2 were matched by primary race, sex, and body mass index (BMI) (±20%) to subjects in Group 1. Both groups were studied concurrently. The rationale for the double-blind, randomized, and placebo-controlled design used for Group 1 (elderly) was to minimize bias on the safety and tolerability objective for this group. A crossover design was chosen to improve sensitivity for detecting safety or tolerability signals in the elderly subjects, particularly in relation to vital signs.

Table 14: Statistical Analysis of the Pharmacokinetic Parameters of Lasmiditan (LY573144) Following a Single Oral Dose of 200 mg Lasmiditan in Elderly and Young Subjects

Analyte: LY573144

Parameter	Treatment	N	Geometric least squares means	Ratio of geometric least squares means 200 mg lasmiditan (Elderly): 200 mg lasmiditan (Young)	90% CI for the ratio (Lower, Upper)
Cmax (ng/mL)	200 mg lasmiditan (Elderly)	18	368	1.21	(0.962, 1.52)
	200 mg lasmiditan (Young)	17	304		
AUC(0-∞) (ng.h/mL)	200 mg lasmiditan (Elderly)	18	2480	1.26	(1.03, 1.55)
	200 mg lasmiditan (Young)	17	1970		
AUC(0-tlast) (ng.h/mL)	200 mg lasmiditan (Elderly)	18	2460	1.27	(1.03, 1.56)
	200 mg lasmiditan (Young)	17	1940		

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time zero to infinity; AUC(0-tlast) = area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration; CI = confidence interval; Cmax = maximum observed drug concentration; N = number of subjects.
Model: Log(PK) = Age_Group

Statistically significant increases in exposure to lasmiditan and metabolites M8 and (S,R)-M18 based on AUC were observed in elderly subjects relative to young subjects, with the 90% CIs for the ratios of geometric least squares (LS) means excluding 1 for all comparisons. Based on AUC(0-∞), exposure was 26% (lasmiditan), 28% (M8), and 50% [(S,R)-M18] higher in elderly subjects compared to young subjects. There were no statistically significant differences in Cmax between age groups for lasmiditan and metabolites M8 and (S,R)-M18, as the 90% CIs for the ratios of geometric LS means spanned unity. No significant differences in tmax were observed for lasmiditan.

Drug-drug interactions: Effect of other drugs on PK of lasmiditan

Several in vitro studies were conducted to evaluate the DDI potential with lasmiditan and to estimate the contribution of CYP and non-CYP enzymes and transporters to the disposition of lasmiditan.

The following enzymes were not involved in metabolism of lasmiditan: MAO-A, MAO-B, FMO-3, CYP450 reductase, xanthine oxidase, alcohol dehydrogenase, aldehyde dehydrogenase, and aldo-keto reductases. Incubations of lasmiditan with a panel of recombinant human CYP enzymes indicated that

CYP2C19 and CYP3A4 were capable of converting lasmiditan to M7. However, M7 accounted for only 7.7% of circulating drug-related material in the human disposition study (Study 110/LAHH) so there is a low risk of lasmiditan being involved in a drug–drug interaction by a CYP inhibitor or inducer. Lasmiditan is a substrate of P-gp in vitro.

Drug-drug interactions: Effect of Lasmiditan on the PK of other drugs

There was no clinically relevant inhibition of the major CYP enzymes by lasmiditan or its 3 major human metabolites (M7, S-M8, and [S,R]-M18). The most potent in vitro inhibition mediated by lasmiditan is competitive inhibition of CYP2D6.

Lasmiditan and its 3 major metabolites are in vitro inducers of CYP2B6 and/or CYP3A4, and M7 was identified as a down-regulator of CYP1A2. However, study LAHE demonstrated that lasmiditan did not alter the PK of midazolam, caffeine, and tolbutamide, which are substrates of CYP3A, CYP1A2, and CYP2C9, respectively.

Lasmiditan was determined to be inhibitor of BCRP and P-gp in vitro.

Population PK analyses

The PK of lasmiditan was additionally investigated with population pharmacokinetic analyses after peroral and iv administration. The following covariates were found to significantly influence lasmiditan PK: body weight on clearance and central volume of distribution, age on clearance and population on volume of distribution. The oral popPK model needs some clarifications (OCs). The lasmiditan IV PK model showed over prediction of lasmiditan concentrations. In addition, no covariate analysis was conducted for the iv data. Since, the PK parameters were fixed from the iv model to estimate the PD parameters, a covariate analysis should be conducted also for the iv model, especially with the covariates shown to be relevant in the oral model. Subsequently, PKPD analyses should be updated with the refined iv model including relevant covariates.

PBPK model for interactions

PBPK models were built to investigate the interaction potential of lasmiditan on CYP2D6 (lasmiditan as inhibitor), PGP (lasmiditan as PGP inhibitor) and CYP3A4 (lasmiditan as CYP3A4 inducer). Induction potential on CYP3A4 was also covered by an in vivo study (LAHE) using midazolam as probe substrate. The PBPK models for CYP2D6 and PGP are not sufficiently validated, therefore no reference to these models should be made in the SmPC.

2.5.2.2. Pharmacodynamics

Mechanism of action

Lasmiditan is a high affinity, centrally-penetrant, 5-hydroxytriptamine 1F (5-HT1F) receptor agonist. The precise mechanism of action is unknown, however, the therapeutic effects of lasmiditan in the treatment of migraine presumably involve agonistic effects at the 5-HT1F receptor, a decrease of neuropeptide release and an inhibition of pain pathways, including the trigeminal nerve.

Primary and Secondary pharmacology

Simulated Driving Performance study 106

A Phase I, Randomized, Double-Blind, Placebo-Controlled, 5-Period, Cross-Over Study Assessing the Effects of Lasmiditan on Simulated Driving Performance in Normal Healthy Volunteers

Study 106 was conducted to determine the effects of acute doses of lasmiditan 50 mg, 100 mg and 200 mg compared to placebo and positive control (alprazolam 1.0 mg) on simulated driving performance in healthy subjects as measured by standard deviation of lateral position (SDLP) using the Cognitive Research Corporation Driving Simulator-MiniSim (CRCDS-MiniSim).

Subjects completed all 5 Periods within the treatment sequence that they were randomized to following a full crossover design. Each Period including washout was approximately 7 days in duration, but no less than 6 days. Study drug was administered by site staff on Day 1 of each Period.

CRCDS-MiniSim testing commenced at 1.5 hours post-dose (on Days 1, 7, 14, 21, and 28 of each Period). The positive control (alprazolam 1.0 mg) was included to establish the sensitivity of the study endpoints to detecting residual sedation.

A total of n=90 healthy subjects (mean age 34.9 years ranging from 22 to 49; 51% female, 49% male), active drivers holding a valid driving license, and having a regular sleep pattern (score < 10 on the Epworth Sleepiness Scale) were included.

The primary endpoint was the Standard Deviation Lateral Position (SDLP) measured by simulated driving performance using CRCDS-MiniSim. The CRCDS CVDA driving scenario, a 62.1 mile (100 km), approximately 60 minute, monotonous, two-lane highway driving task that includes a secondary visual vigilance task (divided attention), was utilized in this study.

Table 15: Standard Deviation of Lateral Position (SDLP) (Units = cm)

	Placebo (N=85)	Lasmiditan 50 mg (N=87)	Lasmiditan 100 mg (N=86)	Lasmiditan 200 mg (N=89)	Alprazolam 1 mg (N=85)
Mean (SD)	28.77 (6.73)	38.52 (12.39)	44.03 (13.55)	50.24 (13.76)	51.48 (14.47)
LSMeans*	29.08	38.94	44.42	50.14	51.78
Median	27.86	34.8	40.75	48.5	47.49
Min, Max	18.82, 57.64	22.88, 84.54	24.18, 88.88	26.98, 87.93	29.08, 86.74
		Lasmiditan 50 mg vs PBO	Lasmiditan 100 mg vs PBO	Lasmiditan 200 mg vs PBO	Alprazolam 1 mg vs PBO
Diff in LSMean*		9.86	15.35	21.06	22.71
95% CI*		7.39, 12.33	12.87, 17.82	18.60, 23.52	20.23, 25.18
p-value*		<.001	<.001	<.001	<.001
		Lasmiditan 50 mg vs Alprazolam 1 mg	Lasmiditan 100 mg vs Alprazolam 1 mg	Lasmiditan 200 mg vs Alprazolam 1 mg	
Diff in LSMean*		-12.85	-7.36	-1.65	
95% CI*		-15.32, -10.38	-9.84, -4.88	-4.11, 0.82	
p-value*		<.001	<.001	0.19	

*Mixed effects model with fixed effects for sequence, period, and treatment, and a random effect for subject within sequence, variance component covariance structure, and Kenward-Roger degrees of freedom. Estimated differences are first treatment label listed minus second treatment label.

Source Data: Table 14.2.1.1 & Listing 16.2.6.1.1

Overall, the study demonstrated a dose-dependent impact of lasmiditan on driving performance as measured by SDLP, lane exceedance, speed deviation, other measures of driving safety, and on an embedded divided attention test. Clinical significance is established by the finding that the 50, 100, and 200 mg doses of lasmiditan (compared to placebo) had an effect on driving that exceeded the a priori driving safety threshold (i.e., 4.4 cm) based on the impairment seen at .05% blood alcohol concentration (BAC). Compared to placebo, lasmiditan 50, 100, and 200 mg had a negative impact on other cognitive and self-report measures, but less than that observed with alprazolam 1.0 mg. Assay sensitivity was demonstrated by the significant findings seen for alprazolam 1.0 mg, a dose estimated to be comparable to 0.15% BAC. Comparison of mean SDLP values for each dose of lasmiditan to alprazolam 1.0 mg demonstrated that lasmiditan was less impairing than alprazolam at the 50 and 100 mg doses but was not statistically different from alprazolam at the 200 mg dose.

Simulated Driving Performance study LAIF - Duration of effect of lasmiditan

A Phase I, Randomized, Subject- and Investigator-Blind, Placebo-Controlled, 4-Period Cross-Over Study Assessing the Duration of Effect of Lasmiditan on Simulated Driving Performance in Healthy Volunteers

Study LAIF was conducted determine the duration of effect of acute doses of lasmiditan 100 and 200 mg compared to placebo on simulated driving performance in healthy subjects.

Subjects were randomized to 1 of 4 treatment sequences, and received doses of 100 mg lasmiditan, 200 mg lasmiditan, 50 mg diphenhydramine, or placebo, in each of 4 cross-over treatment periods. Study treatments were administered at up to 4 dosing occasions (0, 6, and 10 hours on Day 1 and 22 hours on Day 2) within each period: single doses of 100 and 200 mg lasmiditan were each administered at 1 occasion (0 hours); 50 mg diphenhydramine (used to establish the sensitivity of the study endpoints) was administered at 3 occasions (2 hours prior to each driving assessment in that period; 6, 10 and 22 hours). Placebo was administered at all other dosing occasions where active drug was not administered to maintain the blind.

Table 16: Standard Deviation of Lateral Position at the 8-Hour Time Point

Timepoint: Day 1, 8 h

Statistic	Placebo (N=67)	100 mg Lasmiditan (N=68)	200 mg Lasmiditan (N=68)	50 mg Diphenhydramine (N=68)
N	67	68	68	68
Mean (SD)	29.90 (6.43)	31.21 (6.73)	31.45 (6.42)	34.56 (8.84)
LS Means*	29.85	30.83	31.61	34.83
Median	29.08	30.79	30.62	32.27
Minimum, Maximum	19.7, 49.0	18.9, 52.7	21.6, 49.3	19.2, 62.5
p-value for period*				0.0052
p-value for sequence*				0.6879
		100 mg Lasmiditan vs Placebo	200 mg Lasmiditan vs Placebo	50 mg Diphenhydramine vs Placebo
Difference in LS Means*		0.98	1.76	4.98
95% CI*		(-0.43, 2.39)	(0.32, 3.20)	(3.58, 6.38)
p-value*		n/a	n/a	<0.0001
Non-inferiority p-value**		<0.0001	0.0002	n/a

Abbreviations: CI = confidence interval; LS = least square; n/a = not applicable; N = number of subjects; SD = standard deviation.
* Mixed effects model with fixed effects for sequence, period, and treatment, with repeated observations for subjects for each of the driving time points, an unstructured covariance structure, and Kenward-Roger degrees of freedom. Estimated differences are first treatment label listed minus second treatment label. P-value tests null hypothesis that difference in LS means = 0 versus alternative hypothesis that difference in LS means • 0.
** Non-inferiority p-value tests null hypothesis that difference in LS means • 4.4 versus alternative hypothesis that difference in LS means < 4.4.

Simulated driving performance, as assessed by SDLP on the CRCDS-MiniSim at 8, 12, and 24 hours post-dose, was non-inferior for 100 and 200 mg lasmiditan relative to placebo. At 8 hours post dose, there was a small impairment of simulated driving performance, the magnitude of which is not associated with clinically meaningful increase in crash risk. At 12- and 24-hours post dose, there was no impairment of simulated driving performance. Assay sensitivity was supported by significant findings on primary and secondary driving endpoints for the active control (50 mg diphenhydramine).

<u>Abuse potential study LAHB</u>

A Randomized, Subject- and Investigator-Blind, Placebo- and Active-Controlled Study to Assess the Abuse Potential of Lasmiditan

Abuse liability study LAHB was a randomized, subject- and investigator-blind, placebo- and active-controlled, crossover study to assess the abuse liability of lasmiditan in recreational poly-drug users. Subjects were considered recreational drug users, if they had ≥10 lifetime non-therapeutic experiences (ie, for psychoactive effects) with CNS depressants (eg, benzodiazepines, barbiturates, zolpidem, propofol, gamma-hydroxy-butyrate etc.), thereof ≥1 within the 12 weeks prior to screening, and ≥1

lifetime non-therapeutic use of another drug class of abuse (eg, opioids, stimulants, dissociatives, or hallucinogens).

To qualify for the Treatment Period of the study, subjects must have demonstrated the ability to discriminate an alprazolam test dose from placebo, using the 100-mm bipolar Drug Liking VAS, as defined by (among other criteria):

- Acceptable placebo response ranging from 40 to 60 (inclusive) on the 100-mm bipolar VAS for Drug Liking "at this moment".
- ≥15-mm increase in "liking" alprazolam more than placebo.

Only subjects who demonstrated the ability to discriminate an alprazolam test dose from placebo were eligible to enter the Treatment Phase. During the Treatment Phase the abuse liability of 100, 200, and 400 mg lasmiditan compared with placebo and positive control, 2 mg alprazolam was evaluated.

Subjects were randomized to 1 of 10 dosing sequences. Each dosing sequence consisted of 5 cross-over dosing periods that evaluated the abuse liability of 1 of the 5 study treatments: placebo, 2 mg alprazolam, 100 mg lasmiditan, 200 mg lasmiditan, and 400 mg lasmiditan.

The Drug Effects VAS Battery, a tool to evaluate the different subjective effects of the abuse liability of the study drug, was used to assess the primary objective. The Drug Effects VAS Battery includes the following scales: Drug Liking and Overall Drug Liking (where 0 = strong disliking and 100 = strong liking); Take Drug Again, Good Effects, and Bad Effects (where 0 = definitely not and 100 = definitely so); Alertness/Drowsiness (where 0 = very drowsy and 100 = very alert); Agitation/Relaxation (where 0 = very relaxed and 100 = very agitated); High (where 0 = not at all high and 100 = extremely high); and Hallucination (where 0 = not at all and 100 = extremely).

Lasmiditan was compared to the positive control, alprazolam, and to placebo using the maximal effect score (Emax) (or minimal effect score [Emin], where appropriate) of the at-the-moment 100-mm bipolar Drug Liking VAS. The remaining questions in the Drug Effects VAS Battery and the Drug Similarity VAS Battery were assessed as secondary endpoints.

Table 17: Statistical Analysis of the Emax of Drug Liking VAS Scale – Study LAHB

Treatment	LS Mean	Difference of LS Means vs Placebo (90% Confidence Interval)	Difference of LS Means Alprazolam vs Lasmiditan (90% Confidence Interval)
Placebo	53.0	—	
2 mg Alprazolam	85.4	32.4 (28.4, 36.4)	—
100 mg Lasmiditan	68.6	15.6 (11.7, 19.6)	16.8 (12.8, 20.8)
200 mg Lasmiditan	73.3	20.3 (16.3, 24.3)	12.1 (8.10, 16.1)
400 mg Lasmiditan	76.6	23.6 (19.6, 27.6)	8.79 (4.80, 12.8)

Abbreviations: E_{max} = maximal effect score; LS = least squares; VAS = Visual Analog Scale.

The results of that analysis confirmed assay sensitivity, with the lower limit of the 90% CI for the difference in LS means between alprazolam and placebo being greater than 15. Similarity of lasmiditan to placebo in terms of Drug Liking scores was not demonstrated. The condition for rejecting the null hypothesis (difference is $\geq$ 14 mm) for pairwise comparisons of LTN doses with placebo was fulfilled since the upper limits of the 90% CIs for the differences in LS means between lasmiditan and placebo were greater than 14 for all 3 doses of lasmiditan tested. Drug Liking Scores between placebo and all LTN doses were not similar.

Dissimilarity of lasmiditan to alprazolam in terms of Drug Liking scores was not demonstrated, since the lower limit of the 90% CI for the difference in LS means between alprazolam and the supra-therapeutic dose of lasmiditan was less than 5. Alprazolam had a higher Emax of Drug Liking scores than the 2 lower doses of lasmiditan, with the lower limits of the 90% CIs for the difference in LS means between lasmiditan and alprazolam being greater than 5 at both doses.

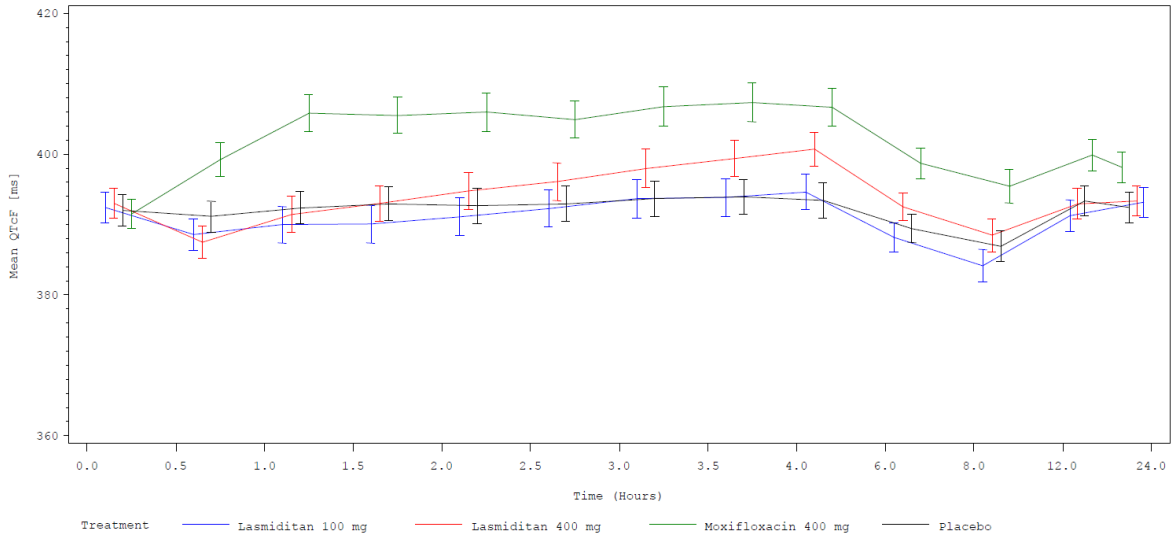
Apart from Drug Liking VAS scores, the results of the Drug Similarity VAS assessments indicated that poly-drug users considered the effects of lasmiditan to be more similar to those of benzodiazepines than those of any other drug class, with mean similarity VAS scores for lasmiditan to benzodiazepines of 57.2 to 74.6 compared to 88.1 for alprazolam to benzodiazepines.

Cardiac De- and Repolarization Duration study LAHP

A Randomized, Double-blind, Placebo-controlled, 4-way Crossover Study to Compare the Effects on the Cardiac De- and Repolarization Duration as well as other Cardiac Safety Parameters of Two Doses of Oral Lasmiditan (100 mg and 400 mg) with those of Moxifloxacin (400 mg) and Placebo in Healthy Subjects

Study LAHP was a randomized, double-blind, placebo- and positive-controlled, double-dummy, 4-way crossover, single-center study of oral Lasmiditan at therapeutic (100 mg) and supra-therapeutic (400 mg) doses, administered as single doses, in healthy adults. Moxifloxacin (a single 400-mg oral dose) was used as a positive control.

Figure 5: QTcF values versus time: Day 1 (Mean, SEM)



Source: CSR Study COL MIG-105/H8H-CD-LAHP dated 10 Sep 2018, Figure 11-8

Mean changes in QTcF from time-matched baseline values on Day 1 between 0.5 and 24 hours were similar for the placebo, 100 mg lasmiditan, and 400 mg lasmiditan treatments at all time points. The upper bound of the 90% CI for ΔQTcF was below 10 ms at every time point. The lower bound of the 90% CI for ΔQTcF was above 5 ms (up to 10.93 ms) for the positive control moxifloxacin from 30 minutes post-dose until 8 hours post-dose.

Gender-related evaluation

For the 400 mg lasmiditan dose, the male subjects showed a shortening of ΔΔQTcF until 2 hours followed by a prolongation up to 6.87 ms (90% CI 4.31, 9.43) at 4 hours with a return to baseline by 8 hours. For the female subjects, a small transient shortening of ΔΔQTcF was seen immediately following dosing

(30 minutes) followed by a prolongation up to 8.03 ms (90% CI 5.40, 10.66) at 3.5 hours, with a return toward baseline by 12 hours.

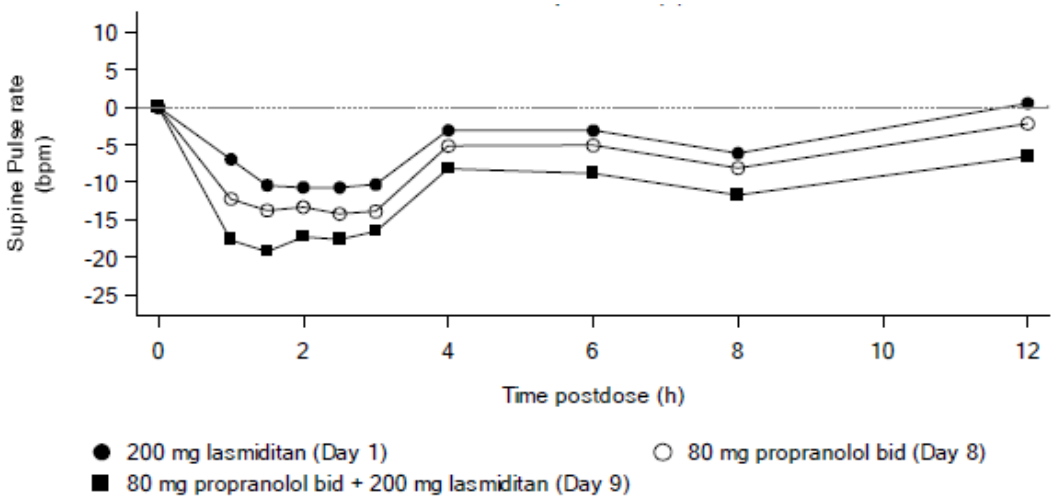
PD interaction study with propranolol on HR and BP (LAHD)

Effect of Lasmiditan on Heart Rate and Blood Pressure in Healthy Subjects Receiving Oral Doses of Propranolol

PD Interaction study LAHD was an open-label, fixed-sequence study in healthy subjects to assess the cardiovascular effects (heart rate, blood pressure) of co-administration of lasmiditan with propranolol. Subjects received a SD of 200 mg lasmiditan on Day 1, then a SD of 200 mg lasmiditan co-administered with steady-state propranolol on Day 9. Propranolol (IR formulation) 80 mg was administered twice daily (bid) on Days 4 through 10.

The cardiovascular effects of LTN alone (Day 1), propranolol alone (Day 8) and LTN SD during propranolol maintenance were assessed through Holter ambulatory monitoring and replicated BP measuring.

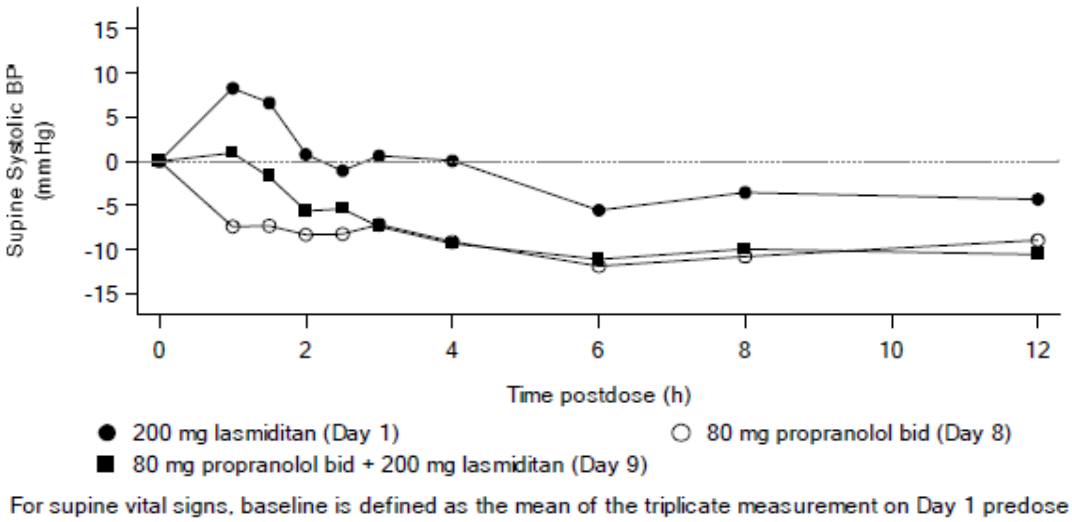
Figure 6: Mean change from baseline in supine vital signs data following a SD of 200 mg lasmiditan or 80 mg bid propranolol administered alone or in combination up to 12 hours post-dose.



For supine vital signs, baseline is defined as the mean of the triplicate measurement on Day 1 predose

Propranolol alone was associated with a maximum mean supine pulse rate decrease of 14.2 bpm. Lasmiditan 200mg alone was associated with a maximum mean transient supine pulse rate decrease of 10.7 bpm. When combined, propranolol and lasmiditan together decreased supine pulse rate by a mean maximum of 19.3 bpm (i.e. an additional lowering of 5.1 bpm compared to propranolol alone). The peak effect occurred at 1 to 2 hours post-dose.

Figure 7: Mean change from baseline in supine vital signs data following a SD of 200 mg lasmiditan or 80 mg bid propranolol administered alone or in combination up to 12 hours post-dose.



For supine vital signs, baseline is defined as the mean of the triplicate measurement on Day 1 predose

An initial increase in mean supine SBP compared to baseline was observed immediately following lasmiditan alone (Day 1), with a maximum mean increase of 8.2 mmHg (1 hour post-dose). The profile indicates a return to baseline values approximately at 2.5 hours post-dose, with a trend for subsequent values to be lower than baseline. Mean supine SBP remained approximately 5 mmHg below baseline from 6 to 12 hours post-dose, with a maximum decrease from baseline of 5.6 mmHg at 6 hours post-dose.

The effect of lasmiditan on vital signs will be discussed in more detail in the safety section based on a pooled analysis across 16 clinical pharmacology studies.

In terms of bioavailability, following co-administration of lasmiditan and propranolol (Day 9), the overall exposure (AUC) to lasmiditan did not change and Cmax decreased by approximately 12%, relative to lasmiditan alone (Day 1). The ratio of geometric LS means were 0.884 (90% CI: 0.832, 0.939), 1.01 (90% CI: 0.967, 1.04), and 1.00 (90% CI: 0.966, 1.04) for Cmax, AUC(0-tlast), and AUC(0-∞), respectively.

PD Interaction study with sumatriptan (LAHU)

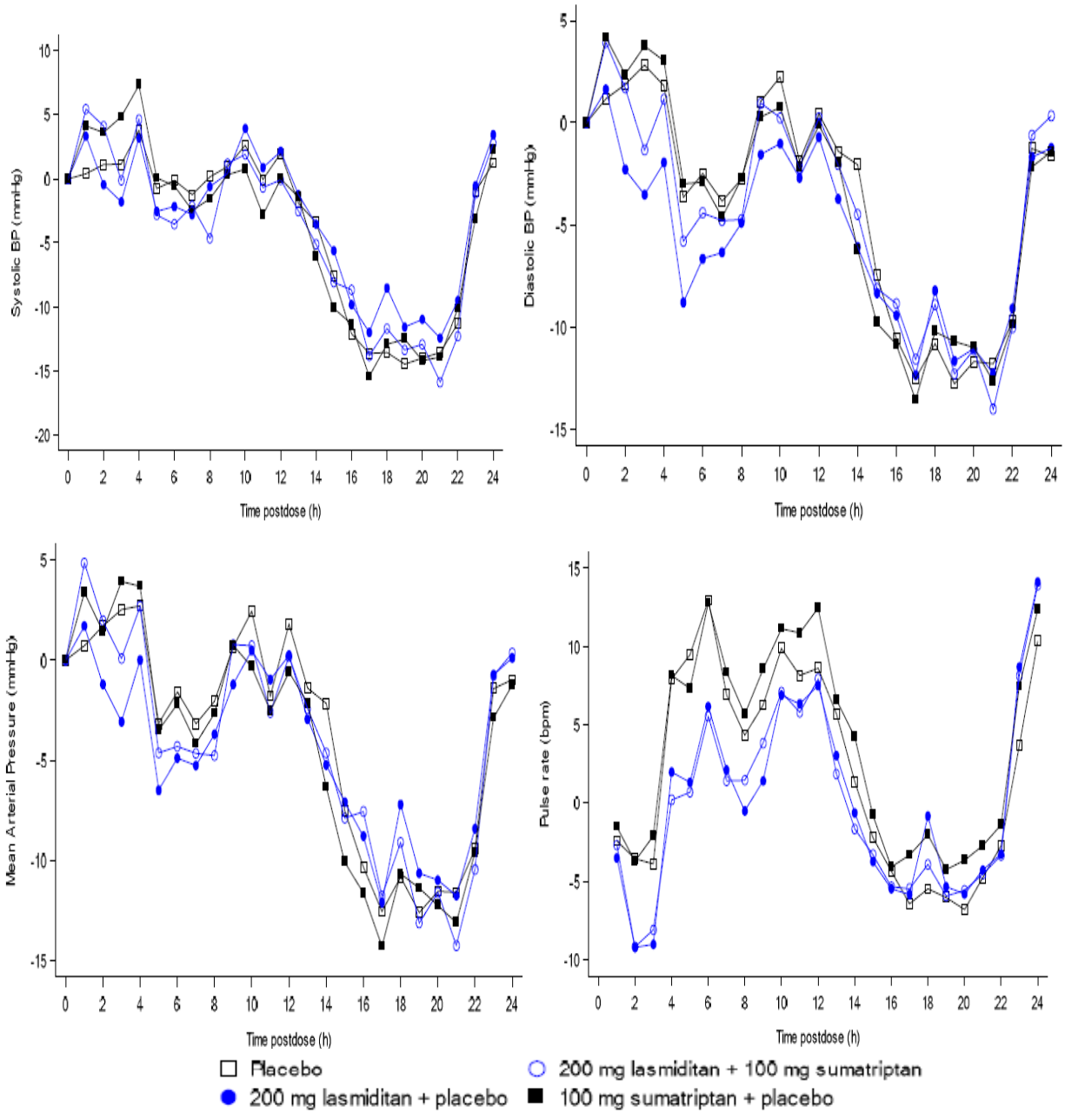
A Randomized, Double-Blind, Four-Period, Crossover Study to Evaluate the Cardiovascular Effect of Single Oral Doses of Lasmiditan when Coadministered with Single Oral Doses of Sumatriptan in Healthy Subjects

PD Interaction study LAHU was a randomized, double-blind (subject- and investigator-blinded), crossover study with 4 study periods in healthy subjects to investigate the cardiovascular effects, PK, and safety and tolerability of oral doses of lasmiditan 200 mg alone, sumatriptan 100 mg alone, and sumatriptan in combination with lasmiditan.

There was a washout of at least 4 days between each dosing day. Apart from PK analysis, the primary parameters for the cardiovascular analyses were peak hourly mean values of systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP), and nadir hourly mean values for pulse rate, and were determined by ABPM. These data were listed and summarized by treatment, along with changes from baseline.

Ambulatory Blood Pressure Monitoring

Figure 8: Arithmetic mean change from baseline in ABPM data following single oral doses of 200 mg lasmiditan, 100 mg sumatriptan, 200 mg lasmiditan + 100 mg sumatriptan, and placebo up to 24 hours post-dose, Study LAHU



Baseline is defined as the mean value during the 2 hours predose for each period

Following administration of lasmiditan alone, sumatriptan alone, and placebo alone, and co-administration of lasmiditan and sumatriptan, mean increases in SBP (3.2 to 3.3 mmHg, 3.6 to 7.3 mmHg, 0.4 to 3.8 mmHg, and 4.1 to 5.4, respectively), DBP (1.6 to 1.6 mmHg, 2.4 to 4.2 mmHg, 1.2 to 2.8 mmHg, and 1.2 to 3.9 mmHg), and MAP (0.0 to 1.7 mmHg, 1.4 to 3.9 mmHg, 0.7 to 2.7 mmHg, and 0.1 to 4.8 mmHg, respectively) were generally observed up to 4 hours post-dose. The initial increases appeared to be similar across all treatments for SBP, DBP, and MAP. Mean decreases in SBP, DBP, and MAP were observed between 12 and 22 hours which also appeared to be similar across all treatments.

Following administration of lasmiditan alone, sumatriptan alone, and placebo alone, and co-administration of lasmiditan and sumatriptan, mean decreases in pulse rate (3.5 to 9.2 bpm, 1.5 to 3.7 bpm, 2.4 to 3.9 bpm, and 2.7 to 9.2 bpm, respectively) were observed up to 3 hours post-dose. The initial decreases appeared to be similar for lasmiditan alone and co-administration of lasmiditan and sumatriptan, and were more pronounced than placebo alone and sumatriptan alone.

Mean increases in pulse rate were observed between 4 and 6 hours post-dose, which appeared to be similar for lasmiditan alone and co-administration of lasmiditan and sumatriptan, and were more pronounced than placebo alone and sumatriptan alone.

In terms of bioavailability, following co-administration of lasmiditan and sumatriptan, the geometric mean value for Cmax, AUC(0-tlast), and AUC(0-∞) for lasmiditan decreased by 7.3%, 3.3%, and 3.1%, relative to lasmiditan alone. The ratios of geometric LS means were 0.927 (90% CI: 0.881, 0.975), 0.967 (90% CI: 0.937, 0.998), and 0.969 (90% CI: 0.939, 1.00) for Cmax, AUC(0-tlast), and AUC(0-∞), respectively.

2.5.3. Discussion on clinical pharmacology

The PK profile of lasmiditan in doses of 50, 100, and 200 mg as IR film-coated tablets was adequately delineated. The compositions of the three tablet strengths are fully proportional, i.e. dose weight multiples.

Lasmiditan is declared to be a BCS class I drug substance. High solubility was shown according to ICH M9 provisions. Mass balance study 110-LAHH examined absorption, metabolism and excretion of LTN in 8 healthy subjects after administration of an oral solution of 200 mg LTN (un-radiolabelled plus [^{14}C]LTN, approx. 100 µCi). Absorption criteria according to ICH M9 were fulfilled since 86.8% of total radioactivity were found in the urine. In-vitro dissolution data show almost complete dissolution within 5 min under the three relevant pH conditions (0.1 N HCl, pH 4.5, pH 6.8). Overall, the claimed BCS class I designation for the 50 mg, 100 mg, and 200 mg dose strengths is justified along ICH M9 Guidance.

The results of ^{14}C mass balance study 110 further indicated that lasmiditan was rapidly absorbed and eliminated with a median tmax of 2 hours and a geometric mean t1/2 of 4.1 hours. Lasmiditan was extensively metabolised, a total of 16 quantifiable metabolites were detected in all matrices examined. Unchanged lasmiditan represented a GM plasma AUC0-∞ value that was only 13.1% of plasma total radioactivity. M7, M8, and (S,R)-M18 were considered major circulating metabolites, with M8 being the predominant metabolite with a GM metabolite to parent ratio of 3.61.

Metabolism of lasmiditan was the primary clearance route, since unchanged lasmiditan in urine accounted for 2.91% of the administered dose, whereas urinary excretion of M8 (CYP independent, ketone reduced, pharmacologically inactive relative to LTN) accounted for 66.1% of the administered dose.

Bioavailability study 103/LAHQ showed that plasma concentration curves after SD administration of 200 mg LTN either as fc tablet or oral solution are almost overlapping. Point estimators for the ratio of Cmax resp. AUC are close to 1. Hence, there was no difference in exposure to LTN between the tablet and solution formulations, consistent with expectations of a BCS Class 1 compound.

Food effect study 104/LAHR pointed to a minor effect of food on exposure to lasmiditan. Ingestion of a standardized high-fat breakfast led to a slight delay of LTN absorption (tmax fasted: 1.5 hours, fed: 2.5 hours) and an increase of about 20% of LTN exposure both in terms of Cmax (1.216 [1.05-1.41]) and AUC0-t (1.186 [1.10-1.28]). According to the posology section of the proposed SmPC, lasmiditan may be taken with or without food. This is acceptable given the fact that the PK profile of LTN was not critically affected by food ingestion and that lasmiditan is to be taken as acute medication in case of a migraine

attack. A post-hoc analysis suggested a possible effect of gender on lasmiditan main PK parameters (Cmax and AUC0-inf). Both genders were equally represented (n=15 each). Irrespective of food intake, an increase of approximately 20-30% in Cmax and 30% in AUC was noted in female subjects compared to male subjects. The observed effect was not driven by body weight. However, the covariate for sex on the apparent central volume of distribution was not significant and was not retained in the final PK model.

In Multiple Ascending Dose (MAD) study LAHE tolerability and PK of LTN was examined after 7-day consecutive dosing of either 200 mg (Cohort 1) or 400 mg (administered as 2 x 200 mg) lasmiditan. At both dose levels plasma concentration curves of LTN were largely similar on Day 1 and Day 7 after repetitive once daily dosing over one week with identical time to maximum plasma concentration (tmax 2 hours) and elimination half lives (t1/2 about 4 hours). Concordant with the short t1/2 elimination values, no accumulation was observed as expressed by accumulation ratios for Cmax and AUC close to 1. The PK properties of LTN do not appear to vary with chronic dosing.

A comprehensive clinical study programme was undertaken to characterize the PK profile of LTN is special populations. Separate studies were conducted in renally resp. hepatically impaired subjects, and the elderly. Furthermore, the potential influence of an acute migraine attack on the PK of lasmiditan was examined in migraine patients.

In hepatic impairment study LAHF, subjects with mild or moderate hepatic impairment were compared with healthy controls after administration of 200 mg SD of LTN. The effect of severe hepatic impairment on lasmiditan plasma levels was not investigated. There were about 18-33% increases in Cmax and increases in AUC of about 10-35% in AUC in patients with mild resp. moderate hepatic impairment relative to healthy controls. The time to maximum plasma concentrations shortens with increasing degree of renal impairment (Tmax: control 2.5 hr, mild impairment 2.0 hr, moderate impairment 1.4 hr). Inversely, the elimination half live (t1/2) increases with increasing degree of hepatic impairment (t1/2: control 5.1 hr, mild impairment 5.7 hr, moderate impairment 7.8 hr). The proposed label specifying that n*o dose adjustment is necessary in patients with mild or moderate hepatic impairment* is acceptable. However, in mass balance study 110-LAHH, metabolism was shown to be the primary clearance route of lasmiditan with a total of 16 quantifiable metabolites that were detected. The impact of hepatic impairment on metabolism patterns and metabolites' PK as a subject of various degrees of hepatic impairment remain unclear.

In Mass balance study 110-LAHH, unchanged lasmiditan in urine accounted for only 2.91% of the administered dose. Accordingly, renal impairment study LAHN followed an adaptive design starting with subjects with severe renal impairment. After analysis of this subgroup versus matched healthy controls further evaluation of the effect of renal impairment on LTN blood levels in subjects with mild or moderate degree of renal impairment could be waived. As could be expected, the effect of severe renal impairment on LTN elimination was minor only, but a 2.5-fold increase in exposure to the major M8 metabolite was found. However, there is no sign for re-transformation of the (ketone reduced) alcohol M8 metabolite to the parent substance. Dose levels (Cmax, AUC) achieved for the M8 metabolite in severe renally impaired subjects in study LAHN were lower than those observed in multiple ascending dose study LAHE after 7-day administration of supra-therapeutic once-daily 400 mg LTN doses. No safety issues were identified in MAD study LAHE in healthy volunteers.

The effect of age on the pharmacokinetics of LTN was examined in the LAHA study comparing group of healthy elderly (mean age 70.6 years [median 69.5 yrs, range 64-82]) with young controls, matched for sex and BMI. After SD administration of 200 mg LTN both the extent (AUC point estimator 1.26 [1.03-1.55]) and rate of absorption (Cmax point estimator 1.21 [0.96-1.52]) were increased in the elderly as compared to young controls. The time for maximum plasma concentration was the same (2 hours), the elimination half life was slightly increased in the elderly (t1/2 elderly: 5.5 hours, young: 4.1 hours). In

pivotal phase III studies no upper age limit was defined for study participation. It was concluded that no dose adjustment is required in the elderly subpopulation.

The purpose of study LAHC was to assess the PK of lasmiditan in migraineurs during acute migraine attacks and during inter-ictal periods. There have been literature reports describing decreased absorption of medication, if taken during acute attacks, e.g. zolmitriptan (Thomsen et al. 1996). The phenomenon was generally attributed to gastric stasis during a migraine attack (Aurora SK et al. 2006. Gastric Stasis in Migraine: More than just a paroxysmal abnormality during a migraine attack. Headache 46:57-63). In the case of lasmiditan, however, a migraine attack appeared to have minimal impact on the overall PK profile. Systemic exposure to lasmiditan, as measured by AUC(0-tlast), AUC(0-∞), and Cmax, following a single oral 200-mg dose was similar when administering lasmiditan during a migraine attack compared with during the inter-ictal period. The time to maximum plasma concentration was similar (tmax: during acute attacks 1.77 hours, inter-ictal period 2.08 hours).

Taking PK data generated in healthy volunteers together with those obtained in special populations (elderly, renal / hepatic impairment, migraineurs) and its metabolic resp. pharmacokinetic interaction potential, it is concluded that the PK characterization for lasmiditan, administered as SD of 50, 100, 200 mg, is adequate.

Lasmiditan is a high-affinity (Ki of 1.85 nM), centrally penetrant, selective human serotonin 1F (5-HT1F) receptor agonist that is believed to exert its therapeutic effects in the treatment of migraine by decreasing neuropeptide release and inhibiting pain pathways at the trigeminal nerve. Early dose ranging (proof-of-concept) data for the use of LTN in the treatment of acute migraine attacks were obtained from study 201 (intravenous use of LTN, group sequential dose escalation from 2.5 mg to 45 mg in n=130 migraine patients).

Abuse liability study LAHB in recreational drug users was conducted after it was shown that lasmiditan penetrates the CNS and adverse events possibly related to abuse have been reported in completed clinical studies. It follows an acceptable standard design for an abuse liability study as concerns the choice of alprazolam as active control, the chosen therapeutic (100 and 200 mg) and supra-therapeutic (400 mg) LTN doses, and the bipolar 100 mm VAS for Drug Liking measurement tool. VAS Drug Liking Scores for the three LTN doses clearly separate from placebo. There was a dose-dependent increase in Drug Liking score during the first 1.5 hours after oral administration of a single dose of lasmiditan, which gradually returned to pre-dose levels by approximately 8 hours post-dose. Drug Liking was highest in subjects receiving 2 mg alprazolam. For the supra-therapeutic 400 mg LTN dose Drug Liking was statistically not dissimilar with the one for the alprazolam 2 mg active control. Recreational drug users described the effects of LTN as most similar with benzodiazepines. TEAEs suggestive of abuse liability were observed (euphoric mood: placebo 10.9%, LTN 100 mg 25.5%, LTN 200 mg 49.1%, alprazolam 2 mg 43.4%; feeling of relaxation: placebo 1.8%, LTN 100 mg 10.9%, LTN 200 mg 7.3%, alprazolam 2 mg 22.6%). Overall, it is concluded that all doses of LTN had a higher abuse liability than placebo but a lower abuse liability than alprazolam. The issue is adequately covered in warning section 4.4 of the SmPC.

Driving impairment

Two driving performance studies were conducted. In both studies the same Standard Deviation Lateral Position (SDLP) primary endpoint was measured, i.e. exceedance from driving lane throughout a 62.1 mile (100 km), approximately 60 minute, monotonous, two-lane highway driving task by simulated driving performance using CRCDS-MiniSim. In the first Study 106 driving performance was tested 90 min post-dose, i.e. during the approximate time of LTN peak concentration. Exceedance from driving lane increased in a dose dependent manner during the simulated driving performance test (exceedance in cm for LTN doses 50, 100, 200 mg over placebo: 9.9, 15.4, 21.1 cm, respectively). Therefore, the a priori safety threshold of 4.4 cm exceedance (corresponding to about 0.05% blood alcohol), was

exceeded indicating a significant driving impairment effect for LTN. For the highest 200 mg LTN doses the deviation from lateral position (SDLP) did not differ from the one observed for the 1 mg alprazolam active control. Significant driving impairment around Tmax (2 – 2.5 hours) was shown across the three LTN doses tested in study 106, corresponding to those proposed for marketing.

The subsequent driving performance study LAIF examined how long driving impairment actually lasts after SD dosing of LTN 100 mg and 200 mg (including sedative antihistamine, short acting diphenhydramine 50 mg as active control). Driving ability was tested by three consecutive driving performance tests conducted at 8, 12 and 24 hours post-dose. Already 8 hours post-dose LTN doses of 100 or 200 mg did not impair driving performance to a relevant degree. It can therefore be concluded that the significant driving impairment found around Tmax of LTN (2 – 2.5 hours post-dose) in study 106 does not last for up to 8 hours post-dose. The driving impairment effect found for lasmiditan is adequately addressed by a warning note in SmPC section 4.4.

PD Interaction

In PD Interaction study LAHD the effect of lasmiditan on heart rate (HR) and blood pressure (BP) in healthy volunteers (HV) receiving oral doses of propranolol was tested. The cardiovascular effects were determined of a SD of 200 mg LTN alone, 2 x 80 mg propranolol maintenance alone, and co-administration of one 200 mg SD of LTN in patients receiving regular propranolol by repetitive vital sign measurement and Holter ambulatory monitoring (supine, standing and orthostatic conditions). For both BP and pulse rate significant effects were observed. Pulse rates decreased. The greatest decrease was noted 1.5 hours post-dose: maximum decreases from baseline 10.7 bpm (LTN), 14.2 (propranolol), 19.3 bpm (co-administration). Hence, there was an additive effect if LTN was administered in subjects receiving regular 2 x 80 mg propranolol. Contrary to the lowering effect on pulse rate (lasting for up to 12 hours), single doses of LTN 200 mg initially increased mean supine SBP (8.2 mmHg at 1 hour post-dose) and mean DBP (5.3 mmHg at 1 hour post-dose) compared to baseline. The profiles indicate a return to baseline values approximately at 2.5 hours post-dose, with a trend for subsequent values to be lower than baseline.

PD Interaction study LAHU examined potential PK / PD interactions between lasmiditan (200 mg) and sumatriptan (100 mg). Using ABPM measuring for up to 24 hours post-dose, increases in SBP were observed for around 4 hours post-administration. Following administration of lasmiditan alone, sumatriptan alone, and placebo alone, and co-administration of lasmiditan and sumatriptan, mean increases in SBP (3.2 to 3.3 mmHg, 3.6 to 7.3 mmHg, 0.4 to 3.8 mmHg, and 4.1 to 5.4, respectively). Compared to placebo, neither lasmiditan nor sumtriptan alone led to any statistically significant changes in peak SBP. Transient peak increases in SBP around 4 hours post-dose were highest in the sumatriptan 100 mg group.

In terms of pulse rate, the initial decreases observed over about 4 hours following dosing with lasmiditan alone and co-administration of lasmiditan and sumatriptan were transient, and of a similar magnitude (LS means of -9.03 and -9.27, respectively). The data therefore suggest that sumatriptan does not cause a further reduction in pulse rate when co-administered with lasmiditan compared to dosing with lasmiditan alone. If administered alone, sumatriptan did not decrease the pulse rate to the same degree. Similar decease in pulse resp. heart rate for lasmiditan and co-administered lasmiditan with propranolol were also observed in PD Interaction study LAHD. In neither of the two interaction studies, relevant changes in bioavailability of lasmiditan or co-administered propranol resp. sumatriptan were observed.

QT Study

The thorough QT study 105/LAHP was conducted in accordance with ICH guidance. Assay sensitivity was demonstrated for moxifloxacin, administered as the positive control. At 400 mg (twice the MDD), lasmiditan does not delay cardiac repolarisation, an effect measured as prolongation of the QT interval.

However, at high doses, lasmiditan can facilitate QTc prolongation in particular in female patients. The description of the pharmacodynamics effect in section 5.1 of the SmPC has been modified to adequately reflect the results of QT study 105/LAHP.

2.5.4. Conclusions on clinical pharmacology

A multitude of phase 1 and 2 studies was conducted. Overall, the PK and pharmacological profile of lasmiditan 50, 100, 200 mg fc tablets was adequately characterized.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study(ies)

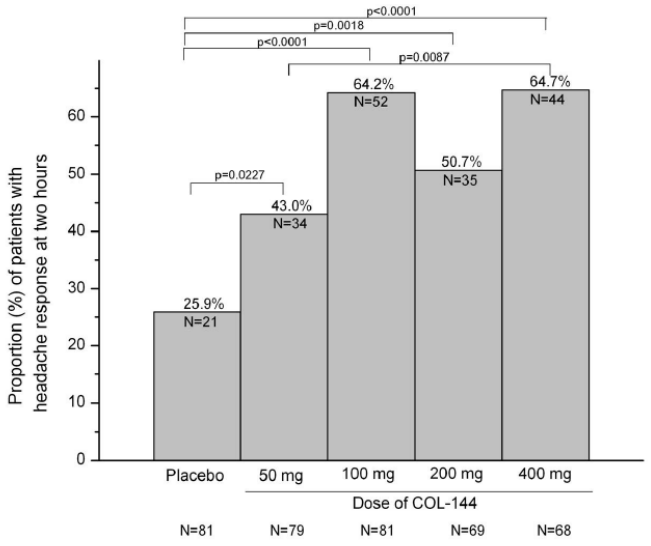
Dose ranging study COL-MIG-202

Based on the dose ranging data obtained from i.v. LTN administration (early PoC study 201, not shown in detail), a further phase II dose ranging study was conducted to treat a single acute migraine attack following a randomized, double-blind, placebo-controlled parallel group design.

A total of N=512 patients were randomly assigned to receive oral COL-144 (50, 100, 200 or 400 mg) or matching placebo (1:1:1:1:1). Eligible patients were asked to treat their next migraine attack within 4 hours of its onset providing that the headache severity was at least moderate at that time and not improving. Patients recorded their response over the next 48 hours using a diary card and were instructed not to use rescue medication until at least 2 hours after taking the study medication. Oral LTN doses were administered as 50 resp. 200 mg tablets or multiples thereof. Eligible patients had to fulfil IHS diagnostic criteria 1.1 and 1.2.1 (2^{nd} edit. 2004) and had to present with a history of migraine for at least one year and at least 1-8 migraine attacks per month. Headache response (defined as reduction in headache severity from moderate or severe at baseline to mild or none 2 hours post-dose) was defined as primary endpoint.

At 2 hours post-dose a higher proportion of patients in the mITT population showed a headache response in the COL-144 groups (43.0% to 64.7%) compared to the placebo group (25.9%).

Figure 9: Proportion of patients with headache response at 2 hours post-dose (mITT, N = 378)



Patients who took rescue medication within the first 2 hours or who failed to record headache severity at 2 hours were assumed to have had no headache response.
Pearson's chi-square test, 2-sided.
mITT = modified intention-to-treat population, N = number of patients.
Data source: Table 3.1A, Appendix 16.2.3.1.

The proportion of patients in the mITT population free of headache 2 hours post-dose was 7.4% in the placebo group and between 13.6% and 27.9% in the COL-144 groups.

Table 18: Number of patients headache-free at 2 hours post-dose (mITT, N = 378)

Treatment group	N total	Number (%)[a] of patients headache-free
Placebo	81	6 (7.4)
50 mg COL-144	79	11 (13.9)
100 mg COL-144	81	11 (13.6)
200 mg COL-144	69	13 (18.8)
400 mg COL-144	68	19 (27.9)

[a] Percentages are based on the total number of patients with available data.
If rescue medication was taken within the first 2 hours, the patient was assumed not to be headache-free at 2 hours.
mITT = modified intention-to-treat population, N = number of patients.
Data source: Table 3.2A, Appendix 16.2.3.2.

The proportion of patients with headache recurrence within 24 hours post-dose was lowest in the 400 mg COL-144 group (50.0%) and ranged across all treatment groups from 50% to 63%.

Table 19: Number of patients with headache recurrence within 24 hours post-dose (mITT, N = 186)

Treatment group	N total[a]	Number (%)[b] of patients with recurrence
Placebo	21	12 (57.1)
50 mg COL-144	34	19 (55.9)
100 mg COL-144	52	30 (57.7)
200 mg COL-144	35	22 (62.9)
400 mg COL-144	44	22 (50.0)

[a] The analysis only includes patients whose headache became mild or pain free at 2 hours after administration of study medication. Patients who used rescue medication within the first 2 hours were excluded from the analysis.
[b] Percentages are based on the total number of patients with available data.
If rescue medication was taken within 24 hours after dosing, even if no headache was reported, headache recurrence was assumed.
mITT = modified intention-to-treat population, N = number of patients.
Data source: Table 3.2C, Appendix 16.2.3.2.

The proportion of patients with associated symptoms like nausea, phonophobia and photophobia decreased in all treatment groups up to 2 hours post-dose with the smallest decrease observed in the placebo group.

2.5.5.2. Main study(ies)

Main studies

The phase III clinical development programme of lasmiditan was designed to show efficacy as an acute treatment for migraine attacks and to demonstrate consistency of effect over multiple attacks. Efficacy data for this submission were drawn primarily from three randomised, double-blind, placebo-controlled Phase 3 trials: Studies 301/LAHJ, 302/LAHK, and LAIJ. Studies 301/LAHJ and 302/LAHK involved treatment of a single migraine attack. Study LAIJ involved the treatment of up to four migraine attacks.

Methods

The two pivotal SD studies in single acute migraine attacks (studies 301 and 302) followed an essentially similar design, thereby enabling definitive conclusions about the efficacy of lasmiditan through independent replication. Their primary objective was to evaluate the efficacy of lasmiditan at 2 hours compared to placebo on migraine headache pain and the most bothersome symptom (MBS) as identified by the individual from the associated symptoms of nausea, phonophobia, and photophobia.

Both were prospective randomized, double-blind, placebo-controlled Phase 3 study in subjects with disabling migraine (Migraine Disability Assessment [MIDAS] score ≥ 11). Subjects were asked to treat a migraine attack with study drug on an outpatient basis. Subjects were stratified (yes or no) for use of concomitant medications that reduced the frequency of migraine episodes.

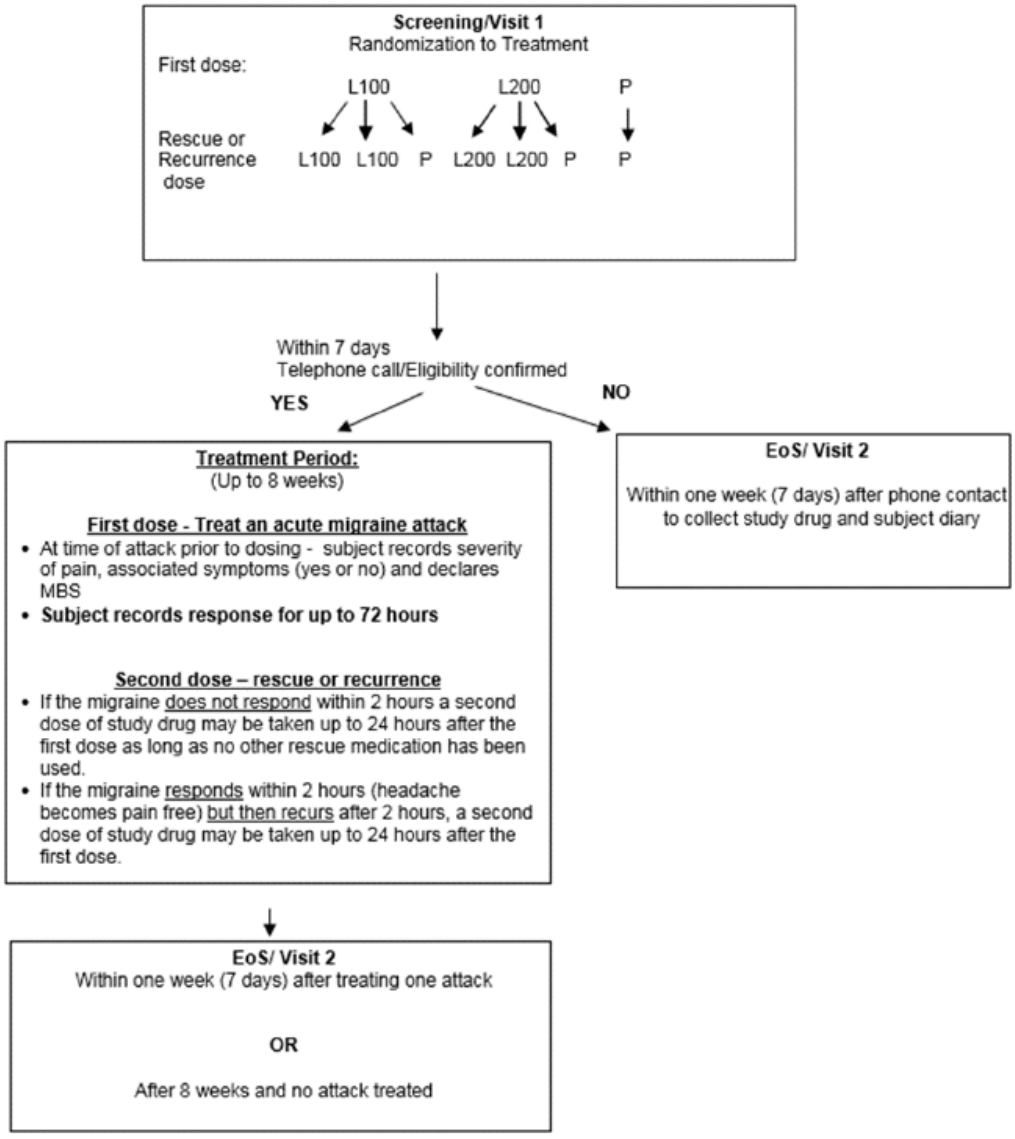
Subjects were instructed to take the study medication within 4 hours after onset as the FIRST treatment for a new migraine attack provided that any aura symptoms had resolved, the headache was either moderate or severe and had been so for less than 4 hours, and no prior analgesic or acute treatment for migraine had been taken to treat the current migraine attack. If the subject had already taken any prior analgesic or other acute treatment for migraine, he/she was no longer eligible to treat the current migraine attack but might have treated a later attack with the study drug.

Subjects recorded their response to the first dose over the next 48 hours using an electronic diary. Subjects were asked not to use rescue medication until at least 2 hours after dosing with study drug and completing the 2 hour assessments. If the migraine did not respond at 2 hours, a second dose of study

drug might have been taken up to 24 hours after the first dose as long as no other rescue medication had been used (second dose as rescue). If the migraine did respond within 2 hours (headache became pain-free) but then recurred after 2 hours, a second dose of study drug might have been taken up to 24 hours after the first dose (second dose for recurrence). Subjects recorded their response to a second dose of study drug, taken for either rescue or recurrence, for 48 hours in the electronic diary. The total time for recording response to study drug was up to 72 hours depending on whether or not a second dose was used.

Subjects were centrally randomized to 1 of 5 treatment sequences to receive lasmiditan 100 mg or lasmiditan 200 mg or placebo for the first dose (in a 1:1:1 ratio) and the second dose for rescue or recurrence of migraine (if needed).

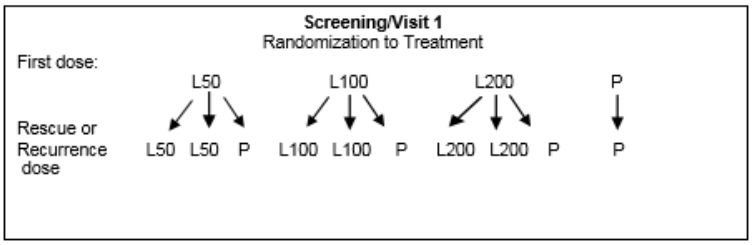
Figure 10: Schematic of Study Design of Study 301



Abbreviations: EoS = End of Study; L100 = lasmiditan 100 mg, L200 = lasmiditan 200 mg; MBS = Most Bothersome Symptom; P = placebo.

Study 302 followed an identical general design. The major difference between the two studies was the range of LTN doses that were tested. In study 302, a third LTN dose (50 mg) was additionally included.

Figure 11: Schematic Dosing Design of Study 302



Apart from single attack trials 301 and 302, consistency of effect across multiple attacks was examined in study LAIJ. This was a prospective, multi-center, randomized, double-blind, placebo-controlled phase 3 study of adult patients suffering from migraine with or without aura. One treatment group received lasmiditan 200 mg for 4 attacks, 1 treatment group received lasmiditan 100 mg for 4 attacks, and a control group received placebo for 3 attacks and lasmiditan 50 mg for 1 attack based on 1 of 2 control treatment sequences.

Table 20: Treatment Group Sequences, Study LAIJ

Treatment Group Sequences	Attack 1	Attack 2	Attack 3	Attack 4
Lasmiditan 200 mg	LTN200	LTN200	LTN200	LTN200
Lasmiditan 100 mg	LTN100	LTN100	LTN100	LTN100
Control 1	Placebo	Placebo	LTN50	Placebo
Control 2	Placebo	Placebo	Placebo	LTN50

Abbreviations: LTN50 = lasmiditan 50 mg; LTN100 = lasmiditan 100 mg; LTN200 = lasmiditan 200 mg.

Participants were informed that no one would receive placebo for all attacks if they treated 4 attacks. During this study, participants were given a period of up to 4 months to treat four migraine attacks with study intervention on an outpatient basis. Participants were randomized in a 1:1:1 ratio to lasmiditan 200 mg, lasmiditan 100 mg, or control.

There was to be at least a 48-hour gap after taking study intervention for the treated attack before treating the next migraine with study intervention.

For migraine attacks which did not meet these criteria or when the participant was unable to treat with study intervention and complete all study procedures during a particular migraine, they could use their usual migraine medication for that migraine and then treat the next appropriate migraine with study intervention. In summary, participants were requested to treat four consecutive appropriate migraine attacks with study intervention, but this was not required if it was not possible.

Study Participants

Studies enrolled patients ≥18 years of age with migraine with or without aura fulfilling the IHS diagnostic criteria 1.1 or 1.2.1, a history of disabling migraine for ≥1 year, and migraine onset prior to 50 years of age. Per the recommendation of the IHS (Tfelt-Hansen et al. 2012; Diener et al. 2019), patients with chronic migraine (≥15 headache days per month) or other forms of primary or secondary chronic headache disorder (e.g., hemicranias continua or medication-overuse headache) were excluded. Patients were required to have 3 to 8 migraine attacks per month (< 15 headache days per month) and a Migraine

Disability Assessment (MIDAS) score ≥11 (indicative of at least moderate disability [interference with normal activities]).

To increase generalisability of the results, patients could participate regardless of previous exposure or response to other migraine drugs, and, in alignment with CHMP guidance, could use concomitant preventive medications if the dose was stable for at least 3 months.

To evaluate safety in patients with cardiovascular risk, which is generally higher in individuals with migraine relative to the general population, the studies did not include an upper age limit and all studies included patients with cardiovascular risk factors such as hypertension, elevated cholesterol, and diabetes (except for those with complications of diabetes). Although Study 301/LAHJ excluded patients with known CAD, clinically significant arrhythmia, or uncontrolled hypertension, Studies 302/LAHK and LAIJ did not exclude these patients.

People with migraine frequently experience depression and anxiety (Buse et al. 2013). The lasmiditan development programme did not have entry restrictions specifically related to psychiatric illness. Allowing inclusion of patients with stable concomitant depression and/or anxiety ensured that the patient population would be similar to that observed in clinical practice. However, all studies excluded patients at imminent risk for suicide or with a recent history of suicide attempt.

Treatments

Subjects were randomly assigned to 100 mg or 200 mg lasmiditan or placebo in single attack study 301. In study 302, an additional 50 mg LTN dose arm was included (see *Methods* above). In studies covering more than 1 attack, like consistency trial LAIJ or open-label long-term study 305, patients were also assigned to 100 or 200 mg LTN without the option for dose adaptation as a function of individual tolerability resp. efficacy during preceding attacks.

Studies 301/302: Rescue Medication

Rescue medication was permitted after completion of the 2-hour assessments if the migraine did not respond (subject is not headache pain-free). If the migraine did not respond within 2 hours, a second dose of randomized study drug may have been taken up to 24 hours after the first dose as long as no other rescue medication had been used. The Investigator advised each subject as to an alternative suitable rescue medication. Triptans, ergots, opioids, and barbiturates MUST NOT have been used for rescue medication within 24 hours of study drug administration. The use of rescue medication was recorded in the subject diary.

Consistency study LAIJ: Rescue or recurrence medication

Between 2 and 24 hours after dosing with study intervention, participants could take their own unexcluded medication for rescue treatment or for treatment of recurrent headache. Contrary to single attack studies 301/302, patients were not given the option of a second dose of study medication (taken as either rescue or for recurrent pain) in consistency trial LAIJ.

Outcomes/endpoints

The primary efficacy endpoint for the 3 pivotal studies was pain freedom at 2 hours following initial dose. Patients were asked to assess and record their pain severity using the IHS 4-point pain severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). Pain freedom was defined as a reduction in pain severity from mild, moderate, or severe at baseline to none.

Efficacy Measures in Studies 301/302

Studies 301 and 302 included the same primary and key secondary efficacy endpoints.

The **primary efficacy endpoint** was the proportion of patients in each group that were pain free at 2 hours post-dose.

The **key secondary endpoint** was MBS freedom at 2 hours post-dose. At baseline, patients were asked to report in the e-diary whether they were experiencing nausea (yes/no), phonophobia (yes/no), and/or photophobia (yes/no), and if so, which was most bothersome to them. The presence/absence of all symptoms, including the MBS, was collected at all time points.

Further relevant endpoints like pain relief, sustained pain freedom at 24 and 49 hours post-dose, time to pain resp. MBS freedom, or use of rescue were assessed as follows.

Table 21: Efficacy Endpoints in Studies 301/LAHJ and 302/LAHK (Excerpt)

Other Endpoints	Pain relief[c] at 2 hours postdose
	Time to pain-free[a] through 24 hours after first dose
	Sustained pain-freedom[d] at 24 and 48 hours postdose based on first dose
	Time to MBS-free[b] through 24 hours after first dose
	Time to pain relief[c] through 24 hours after first dose
	Presence of associated symptoms of migraine (vomiting, nausea, photophobia, phonophobia) at 2 hours postdose
	Interference in daily activities (disability) at 2 hours postdose
	PGIC at 2 hours post-dose
	Pain recurrence up to 48 hours
	Use of rescue or recurrence medication within 24 hours post first dose
	Headache pain-free[a] after a second dose, separately for rescue and recurrence
	MBS-free[b] after a second dose at 2 hours, separately for rescue and recurrence
	Pain relief[c] after a second dose at 2 hours for recurrence
	Time from first dose to second dose of study medication for recurrence

Abbreviations: MBS = most bothersome symptom; PGIC = Patient Global Impression of Change.

a Pain-free defined as mild, moderate, or severe headache pain becoming none.

b MBS free defined as freedom from patient designated most bothersome symptom of nausea, phonophobia, and/or photophobia.

c Pain relief defined as moderate or severe headache pain becoming mild or none and mild pain becoming none.

d Sustained pain freedom during first attack defined as pain-free at 2 and 24 hours, and 2 and 48 hours, respectively, with no rescue medication.

Efficacy Measures in Study LAIJ

The **primary efficacy endpoints** were the proportion of patients in each group that were pain free at 2 hours post-dose during the first attack, and at 2 hours post-dose in at least 2 out of 3 attacks.

Consistency trial LAIJ covered treatment of 4 migraine attacks. Endpoints either referred to efficacy in 2 out of 3 attacks or 3 out of 4 attacks.

The population for the 2 out of 3 consistency endpoint with sufficient number of successes or failures was defined as all participants who experienced at least 2 successes or 2 failures during their first 2 or 3 mITT-evaluable attacks (for mITT consistency).

Statistical methods

For the Phase 3 studies, the ITT populations included those patients who took at least 1 dose of study drug, and had any post-dose efficacy assessments (Studies 301 and 302) or had any post-dose pain assessments at or before 2 hours (Study LAIJ). The inclusion of these patients in the intent-to-treat (ITT) populations is generally consistent with the definition of the full analysis set according to IHS guidance (Diener et al. 2019).

The prespecified analyses in the pivotal Phase 3 studies differed with respect to the populations assessed for primary and key secondary analyses. Consistent with IHS guidance, the Phase 3 studies requested

that patients treat their migraine with study drug within 4 hours of pain onset. The modified intent-to-treat (mITT) population was used for the primary and key secondary analyses in Studies 301/302; this population included patients treating attacks within 4 hours of pain onset and having any post-dose efficacy assessments.

The inclusion of patients with post-dose pain assessments at or before 2 hours post-dose in the ITT population of Study LAIJ was because the critical efficacy data was collected during this time frame and prior to other medications being allowed for rescue or recurrence. Accordingly, in Study LAIJ, the ITT population used for the primary efficacy analyses included patients who treated an attack of at least mild pain severity with any post-dose pain severity assessments at or before 2 hours post-dose.

The primary and key secondary efficacy analyses were performed on the ITT, mITT, and PP populations. The primary analysis population was the mITT population. Exploratory efficacy analyses were performed on the ITT and ITT-2nd dose populations, depending on the endpoint.

The primary analyses compared the proportion of subjects who were headache pain-free and the proportion of subjects who were MBS-free at 2 hours in the lasmiditan 200 mg and placebo groups in the mITT population. Each of these 2 analyses was carried out using logistic regression Wald Chi-square test with region included in the model and were conducted using a 1-sided test at the alpha = 0.025 level of significance.

Analyses of Efficacy Measures

Studies 301/LAHJ and 302/LAHK

The population for the primary efficacy analysis was the mITT population; all other efficacy analyses were conducted in the ITT or ITT-second dose populations.

Tests of the primary and key secondary endpoints were conducted at a 1-sided significance level of 0.025; tests of all other endpoints were conducted at a 2-sided significance level of 0.05.

Studies 301 and 302 tested the primary, key secondary, and other endpoints using a logistic regression model that included treatment group and concomitant use of migraine prophylaxis medications as covariates. In both studies, for treatment comparisons, an estimate of the odds ratio of achieving a response, as well as the corresponding confidence interval (CI) and p-value using Wald's chi-square test were computed.

Additional analyses were performed to evaluate the efficacy of a second dose (for rescue or recurrence of migraine). Between 2 and 24 hours after the first dose of study drug, patients were allowed to take a second dose of study drug for rescue or recurrence of migraine attack. After taking a second dose of study drug, data relative to first dose were no longer collected; instead, data relative to the time of second dosing were collected.

Study LAIJ

For efficacy analyses, patients were evaluated by attack and by the group to which they were randomised. The populations for the primary efficacy analyses were the ITT population and the ITT-consistency population.

The co-primary measurement of the proportion of patients achieving pain freedom at 2 hours post-dose during the first attack was performed on the ITT population.

The co-primary endpoint of the proportion of patients in each group that were pain-free at 2 hours post-dose in at least 2 out of 3 attacks was performed using the ITT consistency population. This set includes all randomized patients who experienced a sufficient number of successes or failures during ITT evaluable attacks. The "sufficient number" was defined as all patients who experienced at least 2 successes or 2

failures during their first 2 or 3 ITT-evaluable attacks. For patients with more than 3 ITT-evaluable attacks, only the first 3 attacks with the same treatment were considered.

Tests of the primary and gated secondary endpoints were conducted at a 1-sided significance level of 0.025 (which corresponds in these cases to a 2-sided 0.05 alpha level); tests of all other endpoints were conducted at a 2-sided significance level of 0.05.

For the co-primary outcomes logistic regression with categorical terms for treatment and geographic region were used to statistically evaluate the proportions of patients achieving migraine headache pain freedom in the first attack for lasmiditan treatment groups versus placebo and also in the consistency analyses comparing lasmiditan treatment groups versus placebo.

Analysis of variance or analysis of covariance (ANCOVA) was used to assess the effect of lasmiditan over placebo or control for continuous endpoints. The model included fixed categorical effect of treatment and country and baseline as covariate.

Results

Participant flow

Study 301

A total of 2231 subjects were randomized, of these 1922 (86.1%) subjects completed the study; 1805 (93.9%) subjects were treated and 117 (6.1%) were not treated. Of the 309 (13.9%) subjects who discontinued prior to the end of study visit, 83.5% (258 subjects) were not treated. The proportion of subjects who discontinued from the study were similar across the treatment groups. The most common reasons for discontinuation from the study were randomization failure (37.2%), lost to follow-up (36.6%), subject request (13.6%), and non-compliance with protocol (9.1%).

Study 302

A total of 3005 subjects were randomized, of these 2617 subjects completed the study (87.1%); 2493 (95.3%) were treated and 124 (4.7%) were not treated. In this study, discontinuation was defined as the failure to return for the follow-up study visit.

There were 373 subjects (12.4%) who discontinued the study. The percentage of subjects who discontinued the study was similar across the treatment groups (L50 mg, 11.6%; L100 mg, 14.9%; L200 mg,11.3%; placebo, 11.9%). The most common reasons for discontinuation from the study were lost to follow-up (123/373 subjects, 33.0%), randomization failure (112/373 subjects, 30.0%), subject request (65/373 subjects, 17.4%) and non-compliance (60/373 subjects, 16.1%).

Consistency Study LAIJ

Definition of study completer: Participants were to be considered study completers after treating 4 migraine attacks or after completing 4 months of study duration regardless of number of treated attacks. Based on this definition, participants that did not treat any migraine attacks could meet the definition of a study completer.

A greater proportion of participants in the lasmiditan 100 mg and 200 mg treatment groups discontinued the study (15.9% and 18.1%) compared to the control group (11.4%). The most common reason for discontinuing the study was due to AE, which occurred in a higher proportion of participants in the lasmiditan 100 mg and 200 mg treatment groups (7.4% and 7.8%) compared with control (1.2%).

Table 22: Disposition Study LAIJ, Safety Population, Double-Blind Period (Excerpt)

Study Disposition, n (%)	LTN 100 mg N=485	LTN 200 mg N=486	Control[a] N=500	Total N=1471
Study disposition				
Completed	381 (78.6)	369 (75.9)	421 (84.2)	1171 (79.6)
Discontinued	77 (15.9)	88 (18.1)	57 (11.4)	222 (15.1)
Continuing study[b]	27 (5.6)	29 (6.0)	22 (4.4)	78 (5.3)

Abbreviations: LTN = lasmiditan; N = number of participants in the population; n = number of participants in the specified category.

[a] Control group includes participants assigned to placebo for 3 attacks and lasmiditan 50 mg for 1 attack (Attack 3 or Attack 4).

[b] Includes participants who did not have a final onsite visit for the double-blind period prior to the data cutoff date.

Baseline data

The 3 study populations were similar and represented a population with migraine likely to seek treatment in primary or specialty care settings. Across studies, a majority of the patients were female. The patients were, on average, in their early forties (range: 18 to 81 years in the all-treated population) and reported an average migraine history of 18.26 years prior to study entry. At baseline, 23.7% of patients reported using migraine preventive medications such as topiramate or propranolol, which is consistent with the finding in the literature that 17% to 31% of patients with episodic migraine are currently prescribed preventive therapies (Diamond et al. 2007; Blumenfeld et al. 2013). Participants enrolled in Studies 301, 302, and LAIJ were required to have at least moderate disability based on MIDAS ≥11; however, the mean MIDAS score at baseline was above 30, within the severe range of disability.

Table 23: Patient Demographics and Disease Characteristics (Excerpt)
Primary Analysis Population Studies 301/LAHJ, 302/LAHK, LAIJ, Pooled

		301/LAHJ N = 1545 mITT	302/LAHK N = 2156 mITT	LAIJ N = 1296 ITT-2h	Pooled N = 5016 ITT-2h
Continuous Variables					
Age (years)		Nx=1545	Nx=2156	Nx = 1296	Nx=5016
mean (SD)		41.7 (12.05)	42.7 (12.67)	41.17 (11.98)	41.87 (12.32)
BMI (kg/m^2)		Nx=1543	Nx=2152	Nx=1295	Nx=5010
mean (SD)		30.5 (7.96)	30.0 (9.06)	27.04 (6.49)	29.41 (8.24)
Duration of migraine history (years)		Nx=1545	Nx=2155	Nx =1296	Nx=5015
mean (SD)		19.1 (12.77)	18.4 (12.88)	16.93 (12.83)	18.26 (12.91)
Average number of migraines per month in past 3 months		Nx=1545	Nx=2155	Nx = 1295	Nx=5014
mean (SD)		5.1 (1.76)	5.3 (2.02)	4.93 (1.53)	5.15 (1.84)
MIDAS Total Score		Nx=1545	Nx=2153	Nx=1285	Nx=5002
mean (SD)		31.3 (21.50)	32.0 (22.90)	31.9 (20.04)	31.8 (21.67)
Total number days with headache in past 3 months		Nx=1545	Nx=2154	Nx=1285	Nx=5003
mean (SD)		17.5 (10.57)	17.4 (10.11)	18.0 (9.66)	17.7 (10.16)
Average headache pain[a] in past 3 months		Nx=1545	Nx=2154	Nx=1285	Nx=5003
mean (SD)		7.5 (1.63)	7.4 (1.64)	7.1 (1.63)	7.4 (1.63)
Categorical Variables		Nx =1545	Nx =2156	Nx= 1296	Nx = 5016
Age (years)	<65	1498 (97.0)	2056 (95.4)	1259 (97.1)	4838 (96.5)
	65-74	45 (2.9)	89 (4.1)	34 (2.6)	162 (3.2)
	75-84	2 (0.1)	11 (0.5)	3 (0.2)	16 (0.3)
	≥85	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gender, n (%)	Female	1287 (83.3)	1823 (84.6)	1088 (84.0)	4235 (84.4)
Family history of CAD, n (%)[b]		Nx=1545	Nx=2156	Nx=3720	Nx=3720
		533 (34.5)	568 (26.3)	N/A	1113 (29.9)
CVRF, n (%)[c]		Nx=1545	Nx=2156	Nx=1296	Nx=5016
0		610 (39.5)	815 (37.8)	542 (41.8)	1997 (39.8)
1		548 (35.5)	797 (37.0)	486 (37.5)	1814 (36.2)
2		319 (20.6)	410 (19.0)	224 (17.3)	953 (19.0)
3		66 (4.3)	128 (5.9)	40 (3.1)	242 (4.8)
4		2 (0.1)	6 (0.3)	4 (0.3)	10 (0.2)
History of migraine with aura, n (%)		Nx=1530	Nx=2146	Nx =1296	Nx=4988
		559 (36.5)	878 (40.9)	482 (37.2)	1914 (38.4)
Use of migraine prevention medications, n (%)		Nx=1545	Nx=2154	Nx =1296	Nx=5014
		394 (25.5)	408 (18.9)	393 (30.3)	1187 (23.7)
Triptans contraindicated, n (%)		Nx=1545	Nx=2156	Nx=1296	Nx=5016
		12 (0.8)	71 (3.3)	28 (2.2)	112 (2.2)
Overall response to most recent triptan		Nx=671	Nx=988	Nx = 812	Nx-2486
None/Poor		163 (24.3)	317 (32.1)	322 (39.7)	808 (32.5)
Good		508 (75.7)	671 (67.9)	490 (60.3)	1678 (67.5)

Cardiovascular Risk Factors at Baseline

A set of cardiovascular risk factors was identified based on guidelines from the ACC/AHA and defined for each patient as present or absent; these included age >40 years, high total cholesterol, low high-density lipoprotein (HDL), smoking, high blood pressure/history of hypertension, and history of diabetes. Smoking history and low HDL were not collected in Study LAIJ; data for those variables are shown for Studies 301 and 302.

Table 24: Summary of CVRFs at Baseline ITT 2-h Population, Studies 301, 302, LAIJ, Pooled

Characteristic (unit)	(N = 5016)
ACC/AHA recommended variables[a], n/Nx (%)	
Age >40 years	2673/5016 (53.3)
Current smoker[b]	503/3474 (14.5)
High total cholesterol (≥240 mg/dL)	542/5003 (10.8)
Low HDL-cholesterol[b] (<40 mg/dL men, <50 women)	1169/3720 (31.4)
High blood pressure (SBP ≥140 mmHg and/or medical history of hypertension at baseline)	1017/5016 (20.3)
Medical history of diabetes mellitus, total, n/Nx (%)	253/5016 (5.0)
Type 1	8 (0.2)
Type 2	172 (3.4)
Type Unspecified	73 (1.5)

Abbreviations: ACC/AHA = American College of Cardiology/American Heart Association; CAD = coronary artery disease; CV = cardiovascular; HDL = high-density lipoprotein; LDL = low-density lipoprotein; N = Number of patient in the analysis population; n = number of patients in specified category; Nx = number of patients with non-missing data; used as denominator; N/A = not applicable; SBP = systolic blood pressure.

[a] American College of Cardiology/American Heart Association guideline-recommended variables for CV risk assessment in adults without diagnosed disease (Goff Jr et al. 2014).

[b] Current smoking status, LDL, HDL, family history of CAD, and postmenopausal status were not assessed in Study LAIJ; hence, denominators reflect populations assessed in Studies 301/LAHJ and 302/LAHK.

Characteristics of Treated Migraine Attacks

The characteristics of treated migraine attacks for the primary analysis populations based on first dose in Studies 301, 302, and LAIJ and for the combined dataset are summarized below. The median time from the start of migraine pain to first dose was slightly later in Study LAIJ than in Studies 301 and 302, and the associated symptoms were also somewhat different, with a higher proportion of patients with nausea in Study LAIJ.

Table 25Characteristics of Treated Migraine Attacks, Primary Analysis Population, Studies 301, 302, LAIJ, Pooled

		301/LAHJ N = 1545 mITT	302/LAHK N = 2156 mITT	LAIJ N = 1296 ITT-2h	Pooled N = 5016 ITT-2h
Continuous Variables					
Time to first dosing from migraine pain start, hours median (Q1, Q3)		1.03 (0.26, 2.04)	0.98 (0.22, 2.00)	1.17 (0.43, 2.25)	1.08 (0.33, 2.25)
Categorical Variables, n (%)					
Baseline migraine severity	Severe	425 (27.5)	623 (28.9)	300 (23.1)	1326 (26.4)
	Moderate	1091 (70.6)	1499 (69.5)	933 (72.0)	3572 (71.2)
	Mild	29 (1.9)	33 (1.5)	63 (4.9)	118 (2.4)
	None	0	1 (<0.1)	0	0
Baseline associated symptoms	Photophobia	1193 (77.2)	1649 (76.5)	876 (67.6)	3742 (74.6)
	Phonophobia	952 (61.6)	1354 (62.8)	664 (51.2)	2993 (59.7)
	Nausea	663 (42.9)	948 (44.0)	649 (50.1)	2265 (45.2)
	Vomiting	36 (2.3)	50 (2.3)	40 (3.1)	125 (2.5)
	None	107 (6.9)	147 (6.8)	130 (10.0)	382 (7.6)
Baseline symptom identified as MBS	Photophobia	773 (50.0)	1090 (50.6)	514 (39.7)	2395 (47.7)
	Phonophobia	317 (20.5)	447 (20.7)	250 (19.3)	1022 (20.4)
	Nausea	348 (22.5)	472 (21.9)	414 (31.9)	1229 (24.5)
	No MBS	107 (6.9)	147 (6.8)	129 (10.0)	381 (7.6)

Abbreviations: ITT-2h = intent-to-treat 2 hours; MBS = most bothersome symptom; mITT = modified intent-to-treat; n = number of patients in each subgroup; N = total number of patients in each group; Q = quarter.
Note: The primary analysis populations were mITT for Studies 301/LAHJ and 302/LAHK, and ITT-2h for Study LAIJ.
Patients with multiple symptoms at baseline who did not identify any of them as MBS were considered to have all recorded symptoms as MBS.

Numbers analysed

Statistical Analysis Populations

For the Phase 3 studies, the ITT populations included those patients who took at least 1 dose of study drug, and had any post-dose efficacy assessments (Studies 301 and 302) or had any post-dose pain assessments at or before 2 hours (Study LAIJ).

The modified intent-to-treat (mITT) population was used for the primary and key secondary analyses in Studies 301/302; this population included patients treating attacks within 4 hours of pain onset and having any post-dose efficacy assessments.

Table 26: Comparison of Key Efficacy Populations for Phase 3 Placebo Controlled Studies of Lasmiditan

Study	Analysis Population for Primary and Key Secondary Endpoints	Analysis Population for Other Endpoints
301/LAHJ	mITT	ITT, ITT-second dose
302/LAHK	mITT	ITT, ITT-second dose
LAIJ	ITT, ITT Consistency	ITT

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat.

The clinical programme included a range of types of study centres. Most sites in Studies 301 and 302 were research centres without particular expertise in migraine, whereas Study LAIJ included a larger proportion of migraine specialty clinics.

Table 27: Patient Demographics and Disease Characteristics, Primary Analysis Population, Studies 301/LAHJ, 302/LAHK, LAIJ, Pooled

		301/LAHJ N = 1545 mITT	302/LAHK N = 2156 mITT	LAIJ N = 1296 ITT-2h	Pooled N = 5016 ITT-2h
Region, n (%)		Nx=1545	Nx=2156	Nx=1296	Nx=5016
	North America	1545 (100.0)	1805 (83.7)	72 (5.6)	3428 (68.3)
	Europe	0	351 (16.3)	1001 (77.2)	1365 (27.2)
	Other	0	0 (0.0)	223 (17.2)	223 (4.4)

The two single attack trials were multi-centre studies conducted either in the US (301: 99 sites in the US) or in US/Europe (302: 125 sites, thereof 97 in US, 16 in Germany, 12 in the UK). Consistency trial LAIJ was conducted at 125 sites and enrolled subjects from 17 countries (US, various EU, Switzerland, Mexico, India, Russia, China). The largest portions of the pivotal study population was either North-American (68.3%) or European (27.3%).

Outcomes and estimation

Primary endpoint: Pain Freedom at 2 hours post-dose

Pain freedom was a primary endpoint in Studies 301, 302, and LAIJ, and was defined as the proportion of patients with mild, moderate, or severe pain at baseline reduced to no pain at 2 hours post-dose. In Studies 301, 302, and LAIJ the proportion of patients who were pain free at 2 hours post-dose was statistically significantly higher for all doses of lasmiditan compared to placebo. The likelihood of achieving pain freedom at 2 hours post-dose was greater with higher doses of lasmiditan.

Table 28: Pain Free at 2 Hours Post-dose, Primary Analysis Population, Studies 301, 302, and LAIJ

	Treatment			
301/LAHJ mITT	**Placebo** **(N = 524)**		**LTN 100 mg** **(N = 503)**	**LTN 200 mg** **(N = 518)**
Patients with mild, moderate, or severe pain recorded at time of dosing	524		503	518
Pain free[a], n (%)	80 (15.3)		142 (28.2)	167 (32.2)
Odds ratio (95% CI) versus placebo	—		2.2 (1.6, 3.0)	2.6 (2.0, 3.6)
P-value versus placebo	—		<.001	<.001
302/LAHK mITT	**Placebo** **(N = 540)**	**LTN 50 mg** **(N = 556)**	**LTN 100 mg** **(N = 532)**	**LTN 200 mg** **(N = 528)**
Patients with mild, moderate, or severe pain recorded at time of dosing	539	556	532	528
Pain free[a], n (%)	115 (21.3)	159 (28.6)	167 (31.4)	205 (38.8)
Odds ratio (95% CI) versus placebo	—	1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	2.3 (1.8, 3.1)
P-value versus placebo	—	0.006	<.001	<.001
LAIJ ITT-2h	**Placebo** **(N =443)**		**LTN 100 mg** **(N =419)**	**LTN 200 mg** **(N =434)**
Patients with mild, moderate, or severe pain recorded at time of dosing	443		419	434
Pain free[a], n (%)	37 (8.4)		108 (25.8)	127 (29.3)
Odds ratio (95% CI) versus placebo	—		3.83 (2.6, 5.7)	4.56 (3.1, 6.8)
P-value versus placebo	—		<0.001	<0.001

Abbreviations: CI = confidence interval; ITT-2h = intent-to-treat 2 hours; LTN = lasmiditan; mITT = modified intent-to-treat; N = number of subjects in the analysis population; n = number of subjects in the specified category.

[a] Pain free was a reduction in pain severity from with mild, moderate, or severe at baseline to none at the indicated assessment time.

Denominators for calculating percentages were the counts of patients with mild, moderate, or severe headache pain recorded at the time of dosing.

At times through 2 hours, patients were not counted as being pain free if they used rescue medication at or before those times.

p-value, odds ratio, and confidence interval were from a 2-sided test from a logistic regression model. For studies 301/LAHJ and 302/LAHK, the model included treatment group and background use of medication to reduce the frequency of migraines as covariates For Study LAIJ, the model included treatment group and geographic region as covariates.

Pain Freedom – Lasmiditan 50 mg

Lasmiditan 50 mg was assessed in single attack Study 302; additionally, in Study LAIJ, patients in the control group received lasmiditan 50 mg or placebo for the third treated or fourth treated attack. In the control group, pain freedom at 2 hours was seen in 12% of patients with placebo and 19.1% of patients with lasmiditan 50 mg, with a therapeutic gain of 7.1% (p=0.015). These results for pain freedom are similar to those observed with lasmiditan 50 mg in single attack study 302.

Table 29: Efficacy of Lasmiditan on Pain Freedom at 2 Hours Post-dose in Trials Including 50 mg

	Study 302/LAHK mITT population				Study LAIJ ITT population Control Group[a] First Attack				
	PBO	LTN 50 mg	LTN 100 mg	LTN 200 mg	PBO	LTN 50 mg	PBO	LTN 100 mg	LTN 200 mg
	N=540	N=556	N=532	N=528	N=275	N=288	N=443	N=419	N=434
n (%)	115 (21.3)	159 (28.6)	167 (31.4)	205 (38.8)	33 (12.0)	55 (19.1)	37 (8.4)	108 (25.8)	127 (29.3)
Therapeutic gain %		7.3	10.1	17.5		7.1		17.4	20.9
Odds ratio (95% CI)		1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	2.3 (1.8, 3.1)		1.83 (1.1, 3.0)		3.83 (2.6, 5.7)	4.56 (3.1, 6.8)
p-value vs placebo		0.003	<.001	<.001		0.015		<.001	<.001

Abbreviations: CI confidence interval; ITT = intent-to-treat; LTN = lasmiditan; mITT – modified intent-to-treat; N = number of subjects in the analysis population.
n = number of subjects in the specified category; PBO = placebo.
[a] Data is from the 3rd and 4th attack in Study LAIJ.
Note: Study 302/LAHK: p-value, odds ratio, and confidence interval were from a 1-sided test from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.
Study LAIJ: p-value, odds ratio, and CI are from a 2-sided test from a logistic regression model with sequence (Control 1/2), treatment (LTN50, Placebo), attack number (3/4), and geographic region as covariates.

Most Bothersome Symptom Freedom at 2 hours post-dose

Most bothersome symptom was a key secondary endpoint in Studies 301 and 302 and an other endpoint in Study LAIJ. Most bothersome symptom free was defined as the absence of the associated symptom of migraine (either nausea, phonophobia, or photophobia) at 2 hour post-dose identified at baseline as the MBS.

In Studies 301, 302, and LAIJ, the proportion of patients who were MBS free at 2 hours post-dose was statistically significantly higher for all doses of lasmiditan compared to placebo, with a dose response observed in Study 302, but not in Studies 301 or LAIJ.

Table 30: MBS free at 2 Hours Post-dose, Primary Analysis Population, Studies 301, 302, and LAIJ

	Treatment			
301/LAHJ mITT	**Placebo (N = 524)**		**LTN 100 mg (N = 503)**	**LTN 200 mg (N = 518)**
MBS recorded at time of dosing, n	488		469	481
MBS free[a], n (%)	144 (29.5)		192 (40.9)	196 (40.7)
Odds ratio (95% CI) versus placebo	—		1.7 (1.3, 2.2)	1.6 (1.3, 2.1)
P-value versus placebo	—		<.001	<.001
302/LAHK mITT	**Placebo (N = 540)**	**LTN 50 mg (N = 556)**	**LTN 100 mg (N = 532)**	**LTN 200 mg (N = 528)**
MBS recorded at time of dosing, n	514	512	500	483
MBS free[a], n (%)	172 (33.5)	209 (40.8)	221 (44.2)	235 (48.7)
Odds ratio (95% CI) versus placebo	—	1.4 (1.1, 1.8)	1.6 (1.2, 2.0)	1.9 (1.4, 2.4)
P-value versus placebo	—	.018	<.001	<.001
LAIJ ITT-2h	**Placebo (N =443)**		**LTN 100 mg (N =419)**	**LTN 200 mg (N =434)**
MBS recorded at time of dosing, n	396		376	395
MBS free[a], n (%)	111 (28.0)		152 (40.4)	154 (39.0)
Odds ratio (95% CI) versus placebo	—		1.74 (1.3, 2.4)	1.63 (1.2, 2.2)
P-value versus placebo	—		<0.001	0.001

Abbreviations: CI = confidence interval; ITT-2h = intent-to-treat 2 hours; LTN = lasmiditan; MBS = most bothersome symptom; mITT = modified intent-to-treat; N = total number of patients in each group; n = number of patients in each subgroup.

[a] MBS free was defined as the absence of the associated symptom of migraine (either nausea, phonophobia, or photophobia) at 2 hour post-dose identified pre-dose as the most bothersome symptom. Patients who recorded that no symptoms were present at time of first dose were excluded from the MBS analysis.

Note: Denominators for calculating percentages were the counts of patients with symptoms (phonophobia, photophobia, or nausea) other than migraine pain recorded at the time of dosing.

At times through 2 hours, patients were not counted as being MBS free if they used rescue medication at or before those times.

p-value, odds ratio, and confidence interval were from a 2-sided test from a logistic regression model. For Studies 301/LAHJ and 302/LAHK, the model included treatment group and background use of medication to reduce the frequency of migraines as covariates. For Study LAIJ, the model included treatment group and geographic region as covariates.

Pain Relief

Pain relief was included in the lasmiditan trials as a secondary endpoint in Studies 301 and 302 and as a gated secondary endpoint in Study LAIJ.

This endpoint was assessed by reduction in pain severity from moderate or severe at baseline to mild or none, or a reduction in pain severity from mild at baseline to none at 2 hours post-dose. In the 3 double-blind studies, the proportions of patients who experienced pain relief at 2 hours post-dose were significantly higher for all doses of lasmiditan compared with placebo. The likelihood of achieving pain relief at 2 hours post-dose was similar for patients in the lasmiditan 100 mg and 200 mg groups in the 3 studies, but was greater with higher doses of lasmiditan relative to the 50 mg group in Study 302.

For detailed results, please refer to the Summary of efficacy Tables.

Onset of Freedom from Pain

For onset of pain freedom, the time point at which each lasmiditan group statistically significantly separated from placebo was assessed. The results indicate that lasmiditan has a rapid onset of effect compared with placebo, detectable at 1 hour post-dose with lasmiditan 100 mg and 200 mg (Studies 301, 302, LAIJ) and at 1.5 hours with lasmiditan 50 mg (Study 302).

Examination of the Kaplan-Meier curves also showed higher probability of pain freedom for each of the lasmiditan doses relative to placebo (please refer to 2.7.3.2). Likewise, higher doses of lasmiditan showed greater probability of pain freedom at each time point relative to lower doses.

For detailed results, please refer to the Summary of efficacy Tables.

Sustained Pain Freedom

Sustained migraine pain freedom was defined as having pain freedom at 2 hours post-dose and at the indicated assessment time, having not used any additional migraine intervention following the first dose. In the 3 studies, the proportions of patients with sustained pain freedom were higher in each lasmiditan treatment group than in the placebo treatment group at both 24 hours and 48 hours, with proportions increasing as the lasmiditan dose increased.

In Study 302, the differences between lasmiditan 50 mg and placebo were not statistically significant at 24 and 48 hours, and the differences between lasmiditan 100 mg and placebo were not statistically significant at 48 hours.

For detailed results, please refer to the Summary of efficacy Tables.

Presence of Associated Symptoms of Migraine at 2 Hours

The presence of photophobia, phonophobia, nausea, and vomiting at 2 hours was assessed for Studies 301, 302, and LAIJ, regardless of whether the patient reported the symptom at baseline. The proportions of patients with photophobia and phonophobia at 2 hours post-dose were statistically significantly lower for lasmiditan doses compared to placebo. In all studies, no differences were observed between lasmiditan and placebo in the proportions of participants with nausea or vomiting at 2 hours.

Data shown exemplified for study 302:

Table 31: Summary of Migraine Symptoms Present at 2 Hours ITT Population, Study 302

302/LAHK ITT	Placebo (N = 576)	LTN 50 mg (N = 598)	LTN 100 mg (N = 571)	LTN 200 mg (N = 565)
Photophobia, n (%)	267 (46.4)	230 (38.5)	191 (33.5)	174 (30.8)
Odds ratio (95% CI) versus placebo		0.7 (0.6, 0.9)	0.6 (0.4, 0.7)	0.5 (0.4, 0.6)
P-value versus placebo		.005	<.001	<.001
Phonophobia, n (%)	208 (36.1)	170 (28.4)	143 (25.0)	134 (23.7)
Odds ratio (95% CI) versus placebo		0.7 (0.5, 0.9)	0.6 (0.4, 0.8)	0.5 (0.4, 0.7)
P-value versus placebo		.004	<.001	<.001
Nausea, n (%)	111 (19.3)	125 (20.9)	103 (18.0)	105 (18.6)
Odds ratio (95% CI) versus placebo		1.1 (0.8, 1.5)	0.9 (0.7, 1.3)	1.0 (0.7, 1.3)
P-value versus placebo		.443	.629	.834
Vomiting, n (%)	5 (0.9)	10 (1.7)	4 (0.7)	8 (1.4)
Odds ratio (95% CI) versus placebo		1.9 (0.7, 5.7)	0.8 (0.2, 3.0)	1.7 (0.5, 5.1)
P-value versus placebo		.229	.749	.373

Abbreviations: CI = confidence interval; ITT = intent-to-treat; ITT-2h = intent-to-treat 2 hours; LTN = lasmiditan; N = total number of patients in each group; n = number of patients in each subgroup.

Note: p-value, odds ratio, and confidence interval are from a 2-sided test from a logistic regression model with treatment group and region as covariates.

Efficacy of Second Dose of Study Drug

Patients in Studies 301 and 302 were randomized at study entry to a placebo-controlled 2-dose sequence that included the potential to re-dose for rescue or recurrence.

Comparisons were conducted for patients who took a second dose of study medication 2 to 24 hours after the first dose for rescue or recurrence.

The most relevant comparisons were between groups randomized to lasmiditan for the first dose and randomized to the same dose of lasmiditan versus placebo for the second dose (e.g., second dose efficacy in patients treated with lasmiditan 100 mg/100 mg versus those treated with lasmiditan 100 mg/placebo).

Recurrence Treated with Study Drug

The results show an advantage for a second dose of lasmiditan for the treatment of recurrence. Specifically, pain freedom was achieved in 50% of patients taking lasmiditan as a second dose for recurrence, compared to 32% of those whose second dose was placebo (p =.147). The rate of MBS-freedom was significantly better, with 70.7% of those taking a second dose of lasmiditan for recurrence achieving freedom from MBS at 2 hours compared to 40.9% of those whose second dose was placebo (p =.022). The rate of pain relief was also significantly better for patients taking lasmiditan as a second dose for recurrence, with 77.1% achieving pain relief, compared to 52.0% of those whose second dose was placebo (p =.030).

Table 32: Summary of Efficacy of Lasmiditan at 2 Hours after Treating for Recurrence, Pooled Data from Studies 301 and 302, ITT-Second Dose Recurrence Population All Lasmiditan Doses Pooled

Pooled, with collapsed dose groups	LTN/PBO	LTN/LTN
Pain free, n (%)	8/25 (32.0)	24/48 (50.0)
Odds ratio versus LTN/Placebo (95% CI)		2.13 (0.77, 5.86)
P-value[a]		.147
MBS free, n (%)	9/22 (40.9)	29/41 (70.7)
Odds ratio versus LTN/Placebo (95% CI)		3.55 (1.19, 10.56)
P-value[a]		.022
Pain relief, n (%)	13/25 (52.0)	37/48 (77.1)
Odds ratio versus LTN/Placebo (95% CI)		3.12 (1.11, 8.78)
P-value[a]		.030

Abbreviations: CI = confidence interval; LTN = lasmiditan; MBS = most bothersome symptom; n = number of patients meeting pain-free or MBS-free criteria as appropriate; PBO = placebo.

[a] Mantel-Haenszel odds ratio and 95% CI.

Recurrence: Patients who achieved pain freedom at 2 hours, but then experienced recurrence of mild, moderate, or severe migraine pain and took a second dose of study drug up to 24 hours from the first dose.

The second dose for recurrence was generally taken with a significant gap between the first and second dose. The median time from first dose to second dose ranged from 9.5 to 19.3 hours for the lasmiditan dose groups. Given the relatively short half-life of lasmiditan (5.8 hours), the first and second doses can be considered largely independent events from a pharmacokinetic (PK) and safety perspective.

Table 33: Time from First to Second Dose by Treatment Group, ITT Second Dose for Recurrence Population, Studies 301 and 302

Time to 2nd Dose (hours)	PBO N=21	LTN 50 mg N=13	LTN 100 mg N=35	LTN 200 mg N=28
Mean (SD)	9.2 (6.78)	12.5 (6.44)	11.4 (7.20)	14.9 (7.94)
Median	7.0	11.3	9.5	19.3
Min	2.0	3.5	2.0	2.6
Max	23.9	23.7	22.9	23.6

Abbreviations: LTN = lasmiditan; PBO = placebo; N = number of patients in each group; SD = standard deviation.

Rescue with Study Drug

In the side-by-side and pooled analyses of the proportion of patients in Studies 301 and 302 who were pain free and MBS free after taking a second dose (lasmiditan or placebo) for rescue, no clear benefit of a second lasmiditan dose for rescue treatment was observed. These results suggest that if a first dose of lasmiditan does not result in pain freedom by 2 hours, a second dose of lasmiditan does not appear to provide additional efficacy.

Consistency of effect (Study LAIJ)

Persistence of efficacy over time was evaluated in Study LAIJ in terms of consistency of pain freedom and pain relief across multiple treated attacks.

Pain Freedom in at Least 2 out of 3 Attacks

In Study LAIJ, the proportion of patients who were pain free at 2 hours post-dose in at least 2 out of 3 attacks was statistically significantly higher for the 100 mg and 200 mg doses of lasmiditan compared to placebo. The likelihood of achieving pain freedom at 2 hours in at least 2 out of 3 attacks was greater with 200 mg compared to 100 mg of lasmiditan.

Table 34: Pain Free at 2 Hours in at Least 2 out of 3 Attacks ITT-Consistency Population, Study LAIJ

	Treatment		
	Placebo (N =443)	LTN 100 mg (N =419)	LTN 200 mg (N =434)
Patients with mild, moderate, or severe pain recorded at time of dosing	373	340	336
Pain free[a], n (%)	16 (4.3)	49 (14.4)	82 (24.4)
Odds ratio (95% CI) versus placebo	—	3.77 (2.10, 6.76)	7.24 (4.13, 12.67)
P-value versus placebo	—	<0.001	<0.001

Abbreviations: CI = confidence interval; LTN = lasmiditan; ITT = intent-to-treat; n = number of patients meeting pain-free criteria; N = total number of patients in each group.

a Pain free was a reduction in pain severity from mild, moderate, or severe at baseline to none at the indicated assessment time.

Note: Denominators for calculating percentages were the counts of patients with mild, moderate, or severe headache pain recorded at the time of dosing.

At times through 2 hours, patients were not counted as being pain free if they used rescue medication at or before those times.

p-value, odds ratio, and CI are from a 2-sided test from a logistic regression model with treatment group and region as covariates.

Exploratory analyses were conducted in the ITT Consistency Population to examine headache pain freedom in 0,1,2,3 or 4 out of the maximum treated 4 attacks in study LAIJ.

Table 35: Summary of Headache Pain-Free at 2 Hours in at Least 3 out of 4 Treated Migraines, ITT Consistency Population, Double-Blind Period, Study LAIJ

	L100 mg (N=325)	L200 mg (N=306)	Control (N=387)
Headache Pain-Free at 2 hours, n (%)			
Have 4 attacks			
0 out of 4 attacks	76 (23.4)	59 (19.3)	122 (31.5)
1 out of 4 attacks	49 (15.1)	45 (14.7)	43 (11.1)
2 out of 4 attacks	20 (6.2)	30 (9.8)	17 (4.4)
3 out of 4 attacks	17 (5.2)	19 (6.2)	5 (1.3)
4 out of 4 attacks	6 (1.8)	9 (2.9)	2 (0.5)
Have 3 attacks			
0 out of 3 attacks	67 (20.6)	54 (17.6)	105 (27.1)
1 out of 3 attacks	29 (8.9)	30 (9.8)	17 (4.4)
2 out of 3 attacks	8*	14*	4*
3 out of 3 attacks	1 (0.3)	5 (1.6)	3 (0.8)
Have 2 attacks			
0 out of 2 attacks	60 (18.5)	55 (18.0)	73 (18.9)
1 out of 2 attacks	30*	21*	11*
2 out of 2 attacks	7*	16*	1*
At least 3 out of 4 attacks	24 (7.4)	33 (10.8)	10 (2.6)
Odds Ratio (95% CI)	3.01 (1.42, 6.40)	4.58 (2.22, 9.47)	
p-value vs Control	0.004	<0.001	

Abbreviations: N = number of subjects in the analysis population; n = number of subjects in the specified category; CI = confidence interval; ITT = intent-to-treat.
* - Not included in consistency analysis.
Headache pain-free is defined as a reduction in pain severity from mild, moderate, or severe at baseline to none at the indicated assessment time.
A subject is not counted as being pain-free at a specific time point if she or he used rescue or recurrence medication at or before the specific time point. P-value, odds ratio, and CI are from a 2-sided test from a logistic regression model with treatment group and region as covariates.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36: Summary of efficacy for Study 301

Title: A **S**tudy of Two Doses of L**A**s**M**iditan (100 mg and 200 mg) Compared to Placebo in the Ac**U**te Treatment of Mig**RAI**ne: A randomized, double-blind, placebo-controlled parallel group study (**SAMURAI**)		
Study identifier	COL MIG-301/H8H-CD-LAHJ (301/LAHJ) clinicaltrials.gov: NCT 02439320	
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel study of a single migraine attack that assessed placebo, 100 mg lasmiditan, and 200 mg lasmiditan. Patients were to take study drug when they had a migraine headache of at least moderate severity that was not improving. A second dose of study medication (active drug or placebo) or other medication was allowed 2 to 24 hours after the initial dose for rescue or recurrence.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment period up to 8 weeks not applicable not applicable
Hypothesis	Superiority	
Treatments groups (first dose/second dose) (Total N=2231)	Placebo (PBO/PBO)	742
	Lasmiditan (LTN) 100mg/PBO	248
	LTN 100mg/LTN 100mg	496
	LTN 200mg/PBO	249
	LTN 200mg/LTN 200mg	496

Endpoints and definitions	Primary endpoint	Pain freedom	Proportion of patients who were pain free at 2 hours following initial dose
	Key Secondary endpoint	Freedom from most bothersome symptom (MBS; as identified by the individual from the associated symptoms of nausea, phonophobia, and photophobia)	Proportion of patients who were MBS free at 2 hours following initial dose
	Other Secondary endpoints	Pain relief	Proportion of patients with pain relief at 2 hours following initial dose
		Sustained pain freedom at 24 hours or 48 hours	Proportion of patients who were pain free at 2 hours following initial dose and again at 24 hours or 48 hours without use of any rescue medication
		Onset of pain freedom	Proportion of patients with given event at times through 2 hours after first dose
Database lock	21 August 2016		

Results and Analysis

Analysis description	**Primary endpoint: Pain freedom at 2 hours after the first dose**			
Population/time point	Modified Intent to treat (mITT) / 2 hours			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=524	LTN 100mg N=503	LTN 200mg N=518
	Patients pain free at 2 h, n (%)	80 (15.3)	142 (28.2)	167 (32.2)
	Odds ratio (95% CI) vs PBO	-	2.2 (1.6, 3.0)	2.6 (2.0, 3.6)
	P-value vs PBO	-	<.001	<.001
Notes	Pain freedom was a reduction in pain severity from mild, moderate, or severe at baseline to none at the indicated assessment time. Denominators for calculating percentages were the counts of patients with mild, moderate, or severe headache pain recorded at the time of dosing. At times through 2 hours, patients were not counted as being pain free if they used rescue medication at or before those times. P-value, odds ratio, and confidence interval were from a 1-sided test from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.			
Analysis description	**Key secondary endpoint (gated): MBS freedom at 2 h after the first dose**			
Population/time point	Modified Intent to treat (mITT) / 2 hours			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=524	LTN 100mg N=503	LTN 200mg N=518
	MBS recorded at baseline, n	488	469	481
	Patients MBS free at 2 h, n (%)	144 (29.5)	192 (40.9)	196 (40.7)
	Odds ratio (95% CI) vs PBO	-	1.7 (1.3, 2.2)	1.6 (1.3, 2.1)

	P-value vs PBO	-	<.001	<.001
Notes	MBS freedom was defined as the absence of the associated symptom of migraine (nausea, phonophobia, or photophobia) at 2 hours post-dose identified as the most bothersome symptom. Patients who recorded that no symptoms were present at time of first dose were excluded from the MBS analysis. Denominators for calculating percentages were the counts of patients with relevant symptoms recorded at the time of dosing. At times through 2 hours, patients were not counted as being MBS free if they used rescue medication at or before those times. P-value, odds ratio, and confidence interval were from a 1-sided test from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.			

Analysis description	**Other secondary endpoint: Pain relief at 2 hours after the first dose**			
Population/time point	Intent to treat (ITT) / 2 hours			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=554	LTN 100mg N=562	LTN 200mg N=555
	Patients with pain relief at 2 h, n (%)	217 (39.2)	304 (54.1)	303 (54.6)
	Odds ratio (95% CI) vs PBO	-	1.8 (1.4, 2.3)	1.9 (1.5, 2.4)
	P-value vs PBO	-	<.001	<.001
Notes	Pain relief is defined as a reduction in pain severity from moderate or severe at baseline to mild or none, or a reduction in pain severity from mild at baseline to none, at the indicated assessment time. Denominators for calculating percentages are the counts of patients with mild, moderate, or severe headache pain recorded at the time of dosing. Patients were not counted as having pain relief if they used rescue medication at or before those times. P-value, odds ratio, and confidence interval are from a 2-sided test from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.			
Analysis description	**Other secondary endpoint: Sustained pain freedom**			
Population/time point	Intent to treat (ITT) / 24 hours or 48 hours (as noted)			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=554	LTN 100mg N=562	LTN 200mg N=555
	Patients with sustained pain freedom at 24 hours, n (%)	42 (7.6)	83 (14.8)	103 (18.6)
	Odds ratio (95% CI) vs PBO	-	2.1 (1.4, 3.1)	2.8 (1.9, 4.1)
	P-value vs PBO	-	<.001	<.001
	Patients with sustained pain freedom at 48 hours, n (%)	42 (7.6)	84 (14.9)	91 (16.4)
	Odds ratio (95% CI) vs PBO	-	2.1 (1.5, 3.2)	2.4 (1.6, 3.5)
	P-value vs PBO	-	<.001	<.001

Notes	Sustained pain freedom was defined as experiencing freedom from headache pain at 2 hours following the first dose and at the indicated assessment time, having not used any migraine medications after first dose. Denominators for calculating percentages are the counts of patients with mild, moderate, or severe headache pain recorded at the time of dosing. P-value, odds ratio, and confidence interval are from a 1-sided test from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates.

Analysis description	**Other secondary endpoint: Onset of effect (pain freedom)**			
Population/time point	Intent to treat (ITT) / multiple time points			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=554	LTN 100mg N=562	LTN 200mg N=555
	0.5 hours	7 (1.3)	12 (2.1)	13 (2.3)
	1 hour	35 (6.3)	54 (9.6)*	76 (13.7)*
	1.5 hours	55 (9.9)	110 (19.6)*	136 (24.5)*
	2 hours	83 (15.0)	163 (29.0)*	176 (31.7)*
Notes	*Statistically significant comparison with placebo from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates. Pain freedom is a reduction in pain severity from mild, moderate, or severe at baseline to none at the indicated assessment time. Denominators for calculating percentages were the counts of patients with mild, moderate, or severe headache pain recorded at the time of dosing. At times through 2 hours, patients were not counted as being pain free if they used rescue medication at or before those times.			

Table 37: Summary of efficacy for Study 302

Title: A **S**tudy of Three Doses of Lasmiditan (50 mg, 100 mg, and 200 mg) Compared to **P**lacebo in the **A**cute T**R**ea**T**ment of Migr**A**i**N**e: A randomized, double-blind, placebo-controlled parallel group study **(SPARTAN)**				
Study identifier	COL MIG-302/H8H-CD-LAHK (302/LAHK) clinicaltrials.gov: NCT 02605174			
Design	Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel study of a single migraine attack that assessed placebo, 50 mg lasmiditan, 100 mg lasmiditan, and 200 mg lasmiditan. Patients were to take study drug when they had a migraine headache of at least moderate severity that was not improving. A second dose of study medication (active drug or placebo) or other medication was allowed 2 to 24 hours after the initial dose for rescue or recurrence.			
	Duration of main phase:	Treatment period up to 8 weeks		
	Duration of Run-in phase:	not applicable		
	Duration of Extension phase:	not applicable		
Hypothesis	Superiority			
Treatments groups (first dose/second dose) (Total N=3005)	Placebo (PBO)/PBP	751	LTN 100mg/LTN 100mg	502
	Lasmiditan (LTN) 50mg/PBO	249	LTN 200mg/PBO	249
	LTN 50mg/LTN 50mg	501	LTN 200mg/LTN 200mg	501
	LTN 100mg/PBO	252		
Endpoints and definitions	Primary endpoint	Pain freedom	Proportion of patients who were pain free at 2 hours following initial dose	

	Key Secondary endpoint	Freedom from most bothersome symptom (MBS; as identified by the individual from the associated symptoms of nausea, phonophobia, and photophobia)	Proportion of patients who were MBS free at 2 hours following initial dose
	Other Secondary endpoints	Pain relief	Proportion of patients with pain relief at 2 hours following initial dose
		Sustained pain freedom at 24 hours or 48 hours	Proportion of patients who were pain free at 2 hours following initial dose and again at 24 hours or 48 hours without use of any rescue medication
		Onset of pain freedom	Proportion of patients with given event at times through 2 hours after first dose
Database lock	21 July 2017		

Results and Analysis

Analysis description	**Primary endpoint: Pain freedom at 2 hours after the first dose**				
Population/time point	Modified Intent to treat (mITT) / 2 hours				
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=540	LTN 50mg N=556	LTN 100mg N=532	LTN 200mg N=528
	Patients pain free at 2 h, n (%)	115 (21.3)	159 (28.6)	167 (31.4)	205 (38.8)
	Odds ratio (95% CI) vs PBO	-	1.5 (1.1, 1.9)	1.7 (1.3, 2.2)	2.3 (1.8, 3.1)
	P-value vs PBO	-	0.006	<.001	<.001
Notes	For definition of Pain freedom at 2 hours after first dose, please refer to study 301.				
Analysis description	**Key secondary endpoint (gated): MBS freedom at 2 h after first dose**				
Population/time point	Modified Intent to treat (mITT) / 2 hours				
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=540	LTN 50mg N=556	LTN 100mg N=532	LTN 200mg N=528
	MBS recorded at baseline, n	514	512	500	483
	Patients with MBS freedom at 2 h, n (%)	172 (33.5)	209 (40.8)	221 (44.2)	235 (48.7)
	Odds ratio (95% CI) vs PBO	-	1.4 (1.1. 1.8)	1.6 (1.2, 2.0)	1.9 (1.4, 2.4)
	P-value vs PBO	-	0.018	<.001	<.001
Notes	For definition of MBS freedom at 2 hours post-dose, please refer to study 301.				
Analysis description	**Other secondary endpoint: Pain relief at 2 hours after first dose**				
Population/time point	Intent to treat (ITT) / 2 hours				
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=576	LTN 50mg N=598	LTN 100mg N=571	LTN 200mg N=565
	Patients with pain relief at 2 h, n (%)	258 (44.9)	332 (55.5)	341 (59.7)	343 (60.7)
	Odds ratio (95% CI) vs PBO	-	1.5 (1.2, 1.9)	1.8 (1.4, 2.3)	1.9 (1.5, 2.4)

	P-value vs PBO	-	<.001	<.001	<.001
Notes	For definition of Pain relief at 2 hours post-dose, please refer to study 301.				

Analysis description	**Other secondary endpoint: Sustained pain freedom**				
Population/time point	Intent to treat (ITT) / 24 hours or 48 hours (as noted)				
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=576	LTN 50mg N=598	LTN 100mg N=571	LTN 200mg N=565
	Patients with sustained pain freedom at 24 hours, n (%)	77 (13.4)	103 (17.2)	102 (17.9)	128 (22.7)
	Odds ratio (95% CI) vs PBO	-	1.3 (1.0, 1.9)	1.4 (1.0, 1.0)	1.9 (1.4, 2.6)
	P-value vs PBO	-	0.072	0.041	<.001
	Patients with sustained pain freedom at 48 hours, n (%)	68 (11.8)	89 (14.9)	86 (15.1)	111 (19.6)
	Odds ratio (95% CI) vs PBO	-	1.3 (0.9, 1.8)	1.3 (0.9, 1.9)	1.8 (1.3, 2.5)
	P-value vs PBO	-	.129	.117	<.001
Notes	For definition of Sustained pain freedom, please refer to study 301.				

Analysis description	**Other secondary endpoint: Onset of effect (pain freedom)**				
Population/ time point	Intent to treat (ITT) / multiple time points				
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=576	LTN 50mg N=598	LTN 100mg N=571	LTN 200mg N=565
	0.5 hours	8 (1.4)	11 (1.8)	8 (1.4)	13 (2.3)
	1 hour	42 (7.3)	43 (7.2)	63 (11.0)*	93 (16.5)*
	1.5 hours	78 (13.6)	107 (17.9)*	124 (21.7)*	158 (28.0)*
	2 hours	123 (21.4)	169 (28.3)*	174 (30.5)*	220 (38.9)*
Notes	*Statistically significant comparison with placebo from a logistic regression model with treatment group and background use of medication to reduce the frequency of migraines as covariates. For the definition of Pain freedom, please refer to study 301.				

Table 38: Summary of Efficacy for Study LAIJ

Title: Randomized Controlled Trial of Lasmiditan Over Four Migraine Attacks (CENTURION)		
Study identifier	H8H-CD-LAIJ (LAIJ) EUDRA CT: 2018-001661-17 / NCT: NCT03670810	
Design	Phase 3, prospective, multicentre, randomised, double-blind, modified parallel, placebo-controlled study of 4 migraine attacks that assessed 100 mg lasmiditan, 200 mg lasmiditan, and placebo. Patients were to take study drug when they had a migraine headache of at least moderate severity that was not improving.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment period up to 16 weeks Not applicable Optional extension addendum allowed open-label treatment for 12
Hypothesis	Superiority	
Treatments groups (Total randomised	LTN 100mg	N=539 (Treated N=485)
	LTN 20mg	N=536 (Treated N=486)

N=1613; Total treated N=1471)	Control (total N)	N=538 (Treated N=500). The control group included patients assigned to placebo for 3 attacks and lasmiditan 50 mg for 1 attack (Attack 3 or Attack 4).	
Endpoints and definitions	Primary endpoints	Pain freedom, 2 hours	Proportion of patients who were pain free at 2 hours post-dose during the first migraine attack
		Pain freedom, consistency	Proportion of patients who were pain free at 2 hours post-dose in at least 2 out of 3 attacks
	Key Secondary (i.e. gated) endpoints, with gated doses shown in parentheses	Pain relief, 2 hours (100mg, 200mg)	Proportion of patients with pain relief at 2 hours during the first attack
		Pain relief, consistency (100mg, 200mg)	Proportion of patients in each group with pain relief at 2 hours post-dose in at least 2 out of 3 attacks (LTN 200 mg and 100 mg versus placebo)
		Pain relief, 1 hour (100mg, 200mg)	Proportion of patients with pain relief at 1 hour post-dose during the first attack
		Pain freedom, 1 hour (200mg)	Proportion of patients with pain freedom at 1 hour post-dose during the first attack
		Sustained pain freedom, 24 hours (100mg, 200mg)	Proportion of patients who were pain free at 2 hours following initial dose and again at 24 hours without use of any rescue medication (LTN 200 mg and 100 mg versus placebo)
		Sustained pain freedom, 48 hours (200 mg)	Proportion of patients who were pain free at 2 hours following initial dose and again at 48 hours without use of any rescue medication (LTN 200 mg versus placebo)
		Among triptan insufficient responders: Pain freedom, 2 hours (100 mg, 200 mg)	Proportion of patients in triptan insufficient response subpopulation who were pain free at 2 hours post-dose during the first migraine attack
Endpoints and definitions, continued	Other secondary endpoints, first attack	MBS freedom, 2 hours (as identified by the individual from the associated symptoms of nausea, phonophobia, and photophobia)	Proportion of patients who were MBS free at 2 hours post-dose during the first attack
	Other secondary endpoints, consistency	Among triptan insufficient responders: Pain freedom, consistency	Proportion of patients in triptan insufficient response subpopulation who were pain free at 2 hours post-dose in at least 2 out of 3 attacks
Database lock	27 July 2020		
Results and Analysis			

Analysis description	**Primary endpoint: Pain freedom at 2 hours after the first dose**			
Population/time point	Intent to treat (ITT) / 2 hours post-dose during first attack			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=443	LTN 100mg N=419	LTN 200mg N=434
	Patients pain free at 2 h, n (%)	37 (8.4)	108 (25.8)	127 (29.3)
	Odds ratio (95% CI) vs PBO	-	3.8 (2.6, 5.7)	4.6 (3.1, 6.8)
	P-value vs PBO	-	<.001	<.001
Notes	For definition of Pain freedom at 2 hours after first dose, please refer to study 301. P-value, odds ratio, and confidence interval were from a 1-sided test from a logistic regression model. The model included treatment group and geographic region as covariates.			
Analysis description	**Primary consistency endpoint: Pain freedom at 2 hours post-dose in at least 2 out of 3 attacks**			
Population/time point	ITT consistency population / multiple attacks			
Descriptive statistics, estimate variability, and estimate of effect	Treatment group	PBO N=443	LTN 100mg N=419	LTN 200mg N=434
	Patients with mild, moderate, severe pain at time of dosing	373	340	336
	Patients pain free in at least 2 out 3 attacks	16 (4.3)	49 (14.4)	82 (24.4)
	Odds ratio (95% CI) vs PBO		3.8 (2.1, 6.8)	7.2 (4.1, 12.7)
	P-value vs PBO		<.001	<.001
Notes	For definition of Pain freedom at 2 hours, please refer to study 301. P-value, odds ratio, and CI are from a 2-sided test from a logistic regression model with treatment group and region as covariates.			

Analysis performed across trials (pooled analyses and meta-analysis)

There is essential overlap in study design and populations across the three pivotal phase III studies supporting the efficacy of lasmiditan. Pooled data (as indicated) were integrated in the presentation and discussion of efficacy data.

2.5.5.3. Clinical studies in special populations

To assess the effects of various demographic, baseline characteristics, and study events on treatment outcome, subgroup analyses are presented for the integrated efficacy dataset (301 and 302 and the first attack from Study LAIJ). Subgroup analyses were performed for proportions of patients who were pain free and MBS free at 2 hours following first dose for subgroups based on the variables sex, race, ethnicity, weight (≥90 kg, <90 kg), region, topiramate or propranolol use while on study ("on prophylaxis"), triptan overall response, triptan use contraindicated, history of migraine with aura (yes/no), CV risk factors at baseline (0 or 1, 2 or more), and time of first dose relative to onset (within 4 hours of onset, more than 4 hours after onset).

No statistically significant subgroup differences were seen with respect to the proportion of patients who were pain free or MBS free at 2 hours following first dose by subgroup, with a few exceptions.

2.5.5.4. Supportive study(ies)

Open Label Assessment of Consistency

An Open-Label, Lon**G**-Term, Safety Study of **LA**smi**DI**tan (100 mg and 200 mg) in the **A**cute **T**reatment **O**f Mig**R**aine (**GLADIATOR**) Study COL MIG 305; NCT02565186

Open label study 305 was conducted to address the need for long-term lasmiditan data. The GLADIATOR study evaluated the safety (primary) and efficacy (secondary) of lasmiditan for the intermittent, acute treatment of migraine attacks for up to 1 year.

Initially, study 305 was planned as a prospective, randomized, open-label study in patients with migraine who had completed one of two randomized, placebo-controlled Phase 3 studies 301 or 302. Patients were stratified (yes or no) at randomization for use of concomitant medications that reduced the frequency of migraine episodes. Patients were asked to treat all migraine attacks with study drug on an outpatient basis for up to 12 months. Within the scope of Addendum 2, lasmiditan naïve subjects were also allowed to enrol in study 305/LAHL.

Irrespective of the dose received in preceding studies 301/302, subjects were newly randomized (1:1) in study 305 to LTN 100 mg or 200 mg. A 50 mg LTN dose arm was not included.

A total of N=2171 patients were randomized, of these N=1981 (91.2%) patients who used at least 1 dose of study drug and had post-dose pain severity or symptom assessments for at least 1 migraine attack, were included in the ITT Population. A mITT subset was used in the analysis of pain-free and MBS-free at 2 hours, for all attacks and by quarter. This included attacks treated within 4 hours of onset, and is intended to provide context for comparison of results with the Phase 3 placebo-controlled single attack studies. The mITT population comprises N=1954 patients and provides data for n=17.329 treated attacks in total (L100 mg: n=8844, L200 mg: 8485).

A total of 970 (47.8%) in the Safety Population patients completed all 12 months of the study. Overall, 1060 patients (52.2%) in the Safety Population discontinued the study; the discontinuation rate was similar between the 100 mg and 200 mg treatment groups (53.0% and 51.5% of patients, respectively). Of the 1060 patients who discontinued, the most common reasons were: patient request (41.8%), AE (24.6%), and lost to follow-up (18.4%).

Pain Freedom at 2 Hours

Across all treated attacks, pain freedom at 2 hours was observed in 29.4% of attacks. Pain freedom at 2 hours was observed in 26.7% of attacks treated with lasmiditan 100 mg, and in 32.2% of attacks treated with lasmiditan 200 mg. The Table below presents a summary of treated migraine attacks that were pain-free at 2 hours after first dose by quarter. The number of attacks treated was greatest in the initial quarter of the trial, and dropped in each subsequent quarter. Results were similar across all 4 quarters of the study. A lower proportion of treated attacks achieved pain free status 2-hours post-dose in the lasmiditan100 mg group than in the 200 mg group.

Table 39: Summary of Pain Freedom for All Treated Migraine Attacks Overall and by Quarter (mITT Population), Study 305/LAHL

Pain Free at 2 hours, n/N (%)	LTN 100 mg N=9966	LTN 200 mg N=9731	All Migraine Attacks N=19,697
Overall	2358/8837 (26.7)	2733/8479 (32.2)	5091/17316 (29.4)
Q1	1115/4080 (27.3)	1312/4015 (32.7)	2427/8095 (30.0)
Q2	558/2133 (26.2)	653/1978 (33.0)	1211/4111 (29.5)
Q3	343/1469 (23.3)	441/1437 (30.7)	784/2906 (27.0)
Q4	342/1155 (29.6)	327/1049 (31.2)	669/2204 (30.4)

Abbreviations: LTN = lasmiditan; mITT = modified intent-to-treat; N = total number of treated migraine attacks; n = total number of migraine attacks at 2 hours postdose.

Denominators for calculating percentages are the counts of treated attacks with mild (1), moderate (2), or severe (3) headache pain recorded at the time of dosing

Headache pain-free is a reduction in pain severity from mild, moderate, or severe at baseline to none at the indicated assessment time. Patients are not counted as being pain-free if they used rescue medication at time points on or before 2 hours.

Analyses in First 20 Attacks

The following Table summarizes the proportion of patients who were pain-free at 2 hours post-dose for migraine attacks 1 to 5, 10, 15, and 20. The results show that similar proportions of patients achieved pain freedom in each attack up through the 20th treated attack in the lasmiditan 200 mg group.

There was more variation in the lasmiditan 100-mg group, with fewer patients achieving pain freedom at 2 hours for later treated attacks. A limitation of this analysis was the notably reduced numbers of patients for attacks 10, 15, and 20. Generally, a lower proportion of patients in the 100-mg group were pain free at 2 hours, compared to those in the 200 mg group, across this subset of treated attacks.

Table 40: Summary of Pain Freedom by Treated Migraine Attacks at 2 Hours, ITT Population, Study 305

Pain Free at 2 hours, n/N (%)	LTN 100 mg N=969	LTN 200 mg N=1012
Migraine Attack 1	317/955 (33.2)	360/983 (36.6)
Migraine Attack 2	255/822 (31.0)	291/875 (33.3)
Migraine Attack 3	216/714 (30.3)	239/753 (31.7)
Migraine Attack 4	172/642 (26.8)	216/661(32.7)
Migraine Attack 5	191/576 (33.2)	187/578 (32.4)
Migraine Attack 10	80/335 (23.9)	95/307 (30.9)
Migraine Attack 15	35/199 (17.6)	57/177 (32.2)
Migraine Attack 20	27/120 (22.5)	35/111 (31.5)

Abbreviations: ITT = intent-to-treat; LTN = lasmiditan; N = total number of treated migraine attacks; n = total number of migraine attacks at 2 hours postdose.

Denominators for calculating percentages are the counts of patients with mild, moderate, or severe headache pain recorded at the time of dosing. Headache pain-free is defined as a reduction in pain severity from mild, moderate, or severe at baseline to none at the indicated assessment time. Patients are not counted as being pain-free if they used rescue medication at time points on or before 2 hours postdose. The table represents the first, second, third, fourth, fifth, 10^{th}, 15^{th}, and 20^{th} treated migraine attacks.

Patients Who Treated 5 or More Attacks

In order to address the attrition noted in the analysis of attacks 1-5, 10, 15, and 20, subgroup analyses were conducted in patients who treated a minimum of 5 attacks. The Table below reports the outcomes for patients who were pain-free at 2 hours for individual migraine attacks. For patients (n=1155) who treated ≥5 migraine attacks, 28.8% of patients treated with lasmiditan 100 mg and 32.8% treated with 200 mg were pain-free at 2 hours after first dose over all attacks treated. Results for each of the first 5

treated attacks show that similar results were obtained across treated attacks, with pain-free results ranging from 27% to 33% for the 100 mg group, and 32% to 38% in the 200 mg group.

Table 41: Summary of Pain Freedom at 2 Hours Among Patients who Treated ≥5 Migraine Attacks, ITT Population, Study 305

Pain Free at 2 hours, n/N (%)	LTN 100 mg N=576	LTN 200 mg N=579
Migraine Attack 1	187/567 (33.0)	210/560 (37.5)
Migraine Attack 2	166/565 (29.4)	192/572 (33.6)
Migraine Attack 3	168/566 (29.7)	182/568 (32.0)
Migraine Attack 4	150/564 (26.6)	195/573 (34.0)
Migraine Attack 5	191/576 (33.2)	187/578 (32.4)
Overall Pain Free, %	28.8	32.8

Abbreviations: ITT = intent-to-treat; LTN = lasmiditan; N = Number of patients that treated 5 or more migraines; n = number of patients in each treatment group.

Denominators for calculating percentages are the counts of patients with mild (1), moderate (2), or severe (3) headache pain recorded at the time of dosing.

Headache pain-free is defined as a reduction in pain severity from mild (1), moderate (2), or severe (3) at baseline to none (0) at the indicated assessment time. At times through 2 hours, patients are not counted as being pain-free if they used rescue medication at or before those times. Percentage for overall response for each patient is calculated by dividing the number of successful responses (response at 2 hours) by total number of attacks treated.

2.5.6. Discussion on clinical efficacy

Design and conduct of clinical studies

A comprehensive data package was provided to show efficacy of lasmiditan (LTN) as an acute treatment for migraine attacks. It includes 3 pivotal double-blind, placebo-controlled studies. LTN may be seen as a first-in-class substance, as no other selective 5-HT1F receptor agonist has been approved yet. To provide a sound database that enables to check for reproducibility, two independent single attack trials (essentially similar in design) were conducted in the US and Europe (studies 301 [N=2.231, US] and 302 [N=3.005, US, UK, Germany]).

Consistency of effect across multiple attacks was analysed in study LAIJ (N=1613). The long-term intermittent use of LTN was examined within the scope of open-label safety study 305, which provides supportive efficacy data in all treated attacks over one year (N=1.954 mITT patients, n=17.329 mITT attacks treated).

Essential aspects of the phase III program like the IHS diagnostic criteria (code 1.1 *Migraine without aura* or 1.2.1 *Migraine with typical aura*), choice of target population, endpoints and mix of proven efficacy in single attacks resp. consistency of effect over four attacks, are concordant with current guideline provisions.

The primary efficacy endpoint for the 3 pivotal studies, i.e. pain freedom at 2 hours following initial dose, is fully concordant with current EMA, resp. IHS Guidance. Patients were asked to assess and record their pain severity using the IHS 4-point pain severity rating scale (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain). Pain freedom was defined as a reduction in pain severity from mild, moderate, or severe at baseline to none.

Prior to dosing, the subject recorded presence or absence of typical migraine associated symptoms like nausea, phonophobia, or photophobia and identified which ONE was most bothersome to them as the MBS. MBS freedom at 2 hours post-dose was measured as key secondary endpoint. Apart from pain freedom at 2 hours for the first attack, the portion of patients pain free at 2 hours in at least 2 out of 3

attacks was specified as co-primary in consistency trial LAIJ. The population for the 2 out of 3 consistency endpoint with sufficient number of successes or failures was defined as all participants who experienced at least 2 successes or 2 failures during their first 2 or 3 mITT-evaluable attacks (for mITT consistency). Overall, the entirety of primary, key secondary and secondary endpoints (pain relief, sustained pain freedom 24 hours- resp. 48 hours post-dose, time to pain- / MBS-freedom, PGIC, interference in daily activities (disability) etc.) were defined along guideline recommendations.

In single attack study 301 subjects were randomized 1:1:1 to treat the acute migraine attack with LTN 100 mg, LTN 200 mg or placebo. In the parallel single attack study 302 an additional 50 mg LTN dose arm was included. No controlled data were generated to support consistency of effect across 4 attacks for the 50 mg LTN dose.

Throughout single attack studies patients had the option to take a second dose up to 24 hours after the first dose in case the patient was pain-free after 2 hours but pain recurred (second dose as recurrence) or if the patient did not respond 2 hours after the first dose (second dose as rescue). The second dose was randomized 2:1 to correspond to the same strength as the first dose or placebo. The importance of placebo response encountered in migraine trials is well established. Inclusion of placebo control in the clinical trial program of LTN is endorsed. On the other side, including an active comparator arm (e.g. triptan) would have been useful to contextualize the clinical effect achieved with LTN, however, is considered not essential and difficult to accomplish in the present case given the differences between LTN and triptans in terms of treating migraine patients with CV comorbidity.

The two single attack studies 301 and 302 were identical in terms of exclusion criteria with the exception of the following three cardiovascular conditions: known coronary artery disease (CAD), clinically significant arrhythmia, or uncontrolled hypertension. While these were excluded in study 301, migraine patients presenting with these CV comorbidities were eligible for participating in study 302 or LAIJ. Study 301 (Apr 2015 – Aug 2016) and study 302 (May 2016 – Jun 2017) were not conducted simultaneously. Gaining insight in LTN's safety profile obtained from study 301 may have influenced the sponsor's decision to define less stringent exclusion criteria in study 302. Patients with less critical CV risks like controlled hypertension, high cholesterol, uncomplicated diabetes etc. were not excluded in either of the studies. It is therefore noted that LTN trials included a subgroup of subjects with CV comorbidity for which the use of triptans would formally be contraindicated.

As concerns baseline demographics, the primary analysis population is considered typically representative of the migraine target population in terms of age (mean of 42 years, 96.5% < 65 years), gender (84.4% female), history of migraine with aura (38.4%), and duration of disease history (mean of 18.3 years). Recruited subjects are rather severely affected by the disease as reflected by the average number of migraines per month in past 3 months at baseline (5.15 [1.84]). Accordingly, about one quarter of subjects was on stable migraine prevention medication (23.7% in the pooled population, highest portion in consistency trial LAIJ: 30.3%). In phase III trials, subjects with a history of chronic migraine (CM) were excluded. The average total number of days with headache in past 3 months (17.7 [10.2]) reported by participants is in line with the episodic migraine (EM) diagnosis.

Along the same lines, disease severity as expressed by the mean migraine disability MIDAS Total Score of 31.8 (21.7) points to severe disability. MIDAS is a 5-item questionnaire evaluating the impact of migraine on a patient's life over the past 3 months. Patients' responses are given as the number of days affected over the past 3 months per item.

Efficacy data and additional analyses

Later stage phase II study 202 delivered the most relevant dose finding data to inform the phase III pivotal trial programme. A total of n=512 migraine patients (with or without aura, IHS diagnostic criteria)

were randomly assigned to receive oral LTN (50, 100, 200 or 400 mg) or matching placebo (1:1:1:1:1) and to treat their next acute migraine attack within 4 hours of its onset. LTN's efficacy was examined along relevant endpoints, i.e. portions of pain-free resp. HA relief 2 hours post-dose, efficacy at early time points, recurrence of pain, and improvement of accompanying bothersome symptoms like nausea, phonophobia or photophobia. In all four LTN dose groups (50, 100, 200, 400 mg) statistically significant higher portions of subjects achieved HA relief 2 hours post-dose over placebo. Increasing the SD of LTN further than 100 mg did not result in higher response rates (HA relief: LTN 50 mg: 43.0%, LTN 100 mg: 64,2%, LTN 200 mg: 50.7%, LTN 400 mg: 64.7%, placebo 25.9%). As compared to the 2-hr HA relief endpoint, the 2-hr pain-free endpoint is harder to achieve. Accordingly, 2-hr pain-free response rates doses were considerably lower (7.4% for placebo, 13.6 to 27.9% across the four LTN dose groups). The same phenomenon is observed when acute migraine attacks are treated with triptans (Ferrari MD et al. 2001). While 2-hr pain-free responses were about equal between the 50 mg (13.9%) and 100 mg (13.6%) dose, response rates increased when the dose was further escalated (200 mg: 18.8%, 400 mg: 27.9%).

The incidence of nausea, phonophobia, and photophobia was numerically lowest in the 100 mg dose arm. However, while all active arms improved bothersome migraine co-symptoms as compared to placebo, the dose response relationship across the four LTN dose arms was rather unclear.

As regards safety, dizziness was reported most frequently (23.2% to 38.0% of patients), followed by fatigue (12.2% to 24.3% of patients). The incidence of paraesthesia increased in a dose-dependent manner (50 mg: 2.4%, 100 mg: 11.0%, 200 mg: 16.9%, 400 mg: 20.0%).

The efficacy data obtained in study 202 were partly inconsistent and did not yield a clear dose-response. For the highest 400 mg dose arm a notable added benefit in terms of efficacy was seen only for the 2-hr pain-free endpoint. On the other side, the incidence of AEs was highest in patients receiving 400 mg LTN. Overall, the Applicant's decision to take over the 50, 100, 200 mg dose of LTN (but not the 400 mg) into subsequent pivotal trials is plausible.

In terms of subject disposition in the pivotal trials, study completion was high in single attack studies (301: 86.1%, 302: 87.1%, similar across study arms), which does not surprise given the shortness of intervention. In the course of multiple attack study LAIJ, 91.2% of subjects treated at least 1, and 49.3% treated the maximum 4 attacks. In long term study 305, discontinuation was considerable (52.2%), however, equally distributed across the two dose arms (L100 mg: 53.0%, L200 mg: 51.5%) and not entirely unexpected given the 12-months duration. The remaining database of N=970 (47.8%) subjects providing efficacy and safety data over a 1-year duration is considered meaningful.

Throughout the pivotal trials, subjects were instructed to take the study medication within 4 hours of onset as the FIRST treatment for a new migraine attack provided that any aura symptoms had resolved, and headache intensity was either moderate or severe and had been so for less than 4 hours. However, 2.4% of migraine attacks treated in the Primary Analysis Population were of mild severity. Notably, an attack with mild pain intensity may still qualify as a valid migraine attack subject to fulfilment of remaining IHS diagnostic criteria.

The majority of treated migraine attacks within the Primary Analysis Population was of moderate (69.5 – 72.0%) or severe (23.1 – 28.9%) intensity. The subjects administered the study medication fairly early, with a median time of 60-70 minutes after the onset of a migraine attack. In more than 90% of all attacks subjects could identify one of the associated symptoms as most bothersome. Photophobia was recorded most often as MBS (47.7%), followed by nausea (24.5%) and phonophobia (20.4%).

Efficacy in single attacks

The common primary endpoint across the two single attack studies 301/302 and consistency trial LAIJ (focused on the first of up to four migraine attacks) showed statistically significant superiority over

placebo across all LTN doses (50, 100, 200 mg). With increasing LTN doses numerically higher portions of subjects were pain free at 2 hours (301: L200 mg: 32.2%, L100 mg: 28.2%, PBO: 15.3%; 302: L200 mg: 38.8%, L100 mg: 31.4%, 50 mg: 28.6%, PBO: 21.3%; LAIJ: L200 mg: 29.3%, L100 mg: 25.8%, PBO: 8.4%). The overall magnitude of effect is in a similar range or somewhat lower as what could be shown for most triptans in previous studies. Across all RCTs including sumatriptan a net (placebo-subtracted) effect of 19% [95% CI 17-22] was calculated for sumatriptan 100 mg. For rizatriptan 10 mg and eletriptan 80 mg net effects over placebo are even considerably higher (around 30%, Ferrari MD 2002). Across the pivotal LTN studies placebo response was not unexpectedly high for the 2-hour pain free endpoint. In absolute figures, the portions of subjects achieving pain freedom at 2 hours was lowest in consistency trial LAIJ. This finding may go along with the observation that in study LAIJ the highest portions of subjects receiving migraine prevention was included (30.3%) and at the same time the highest portion of subjects reported none/poor response to most recent triptan at baseline (39.7%).

Along the same lines, for the key secondary endpoint, statistically more patients achieved MBS freedom at the 2-hour assessment time point across all LTN dose arms (50, 100, 200 mg) as compared to placebo. In absolute figures, the portions of patients achieving pain relief across doses and double-blind studies are higher (54-65%) as compared to portions observed for pain freedom (26-39%), which could be expected given that pain relief is considered easier to achieve than pain freedom. If compared to placebo, statistical superiority could be demonstrated for each LTN dose arm (50,100,200 mg) across studies 301/302/LAIJ.

The onset of pain relief is a crucial aspect of efficacy. The portions of patients achieving pain freedom were assessed based on their e-diary entries at 0,5-hours intervals post-dose. One hour after IMP intake the 100 and 200 mg LTN dose arm statistically significant separated from placebo. As time post-dose progressed, the portions of patients reporting to be pain-free increased per dose arm until the 2-hour post-dose primary assessment time point. For the lowest 50 mg LTN dose arm, statistically more patients reached pain freedom from 1.5 hours post-dose onwards. The benefit of early intervention in the course of a migraine attack was previously established in triptan therapy.

Recurrence of pain

In migraine therapy, recurrence of pain is observed in a subgroup of patients, i.e. these subjects respond at the 2-hours primary assessment time point (i.e. are pain free 2 hours post-dose), however, pain recurs within the subsequent course of 24 resp. 48 hours post-dose. To address efficacy in this subgroup of patients the secondary endpoint of sustained pain freedom 24 resp. 48 hours post-dose was examined. As delineated above, it can roughly be observed that about one third of subjects was pain free at 2 hours (primary endpoint, mITT). About half of those 2-hour pain free responders actually reports sustained pain freedom over 24 (24 hours sustained pain free: 301: 14.8% [100 mg], 18.6% [200 mg]; 302: 17.9% [100 mg], 22.7% [200 mg], ITT) resp. 48 hours (48 hours sustained pain free: 301: 14.9% [100 mg], 16.4% [200 mg]; 302: 15.1% [100 mg], 19.6% [200 mg], ITT). Hence, the vast majority of migraine patients sustained pain free at 24 hours, is also pain free at 48 hours. Across LTN dose arms and pivotal trials (301, 302, LAIJ) lasmiditan demonstrated placebo superiority apart from the 50 mg dose examined in study 302 (50 mg vs placebo: at 24 hours p=0.072, at 48 hours p=0.129) and the 100 mg dose arm in study 302 for 48 hours (p=0.117). However, the LTN 100 mg significantly separated from placebo at 24 hours (p=0.041). Interpretation of results for the sustained pain free endpoint should take into account that in PK studies lasmiditan was eliminated with a mean t1/2 value of about 5.7 hours. Furthermore, the sustained pain free secondary endpoint was assessed only in those patients having not used any additional migraine intervention following the first dose.

Presence of photophobia, phonophobia and/or nausea

The presence of photophobia, phonophobia, nausea, and vomiting at 2 hours was assessed for studies 301, 302, and LAIJ, regardless of whether the patient reported the symptom at baseline resp. categorized

the associated symptom as most bothersome. While all doses of LTN (50, 100, 200 mg) statistically significantly reduced the portions of subjects with presence of photophobia or phonophobia as compared to placebo at 2 hours post-dose, other associated symptoms like nausea or vomiting were virtually unaffected by lasmiditan. The portions of subjects reporting vomiting are very low (1-2% across studies), however, a meaningful portion of subjects was nauseous at 2 hours post-dose (about 18-23% across studies 301/302). One may hypothesize that the differential effect of LTN on the different migraine associated symptoms (phonophobia / photophobia on the one side, nausea / vomiting on the other side) could be explained by different pathophysiological mechanisms causing the associated symptoms, with the one being affected by 5-HT1F agonism while the others aren't. Nausea was identified as most bothersome in 24.5% of attacks in the pooled population (301: 22.5%, 303: 21.9%, LAIJ: 31.9%).

Second dosing for recurrence

Second dosing for recurrence was defined for patients who were pain free at 2 hours and then took a second dose of study drug between 2 and 24 hours after first dose. The number of people who took a second dose of study medication for recurrence in the 2 trials (Studies 301 and 302) and had second dose efficacy data was limited (n = 93 total; n = 73 with lasmiditan as the first dose). The results show a numerical advantage for a second dose of lasmiditan for the treatment of recurrence.

To contextualize the number of n=73 affected subjects, it is considered helpful to illustrate the flow of patients. The ITT population of subjects receiving LTN as first dose within the single attack studies 301/302 is composed of N=2851 subjects. Of these, n=902 subjects were pain free at 2 hours and are therefore potentially eligible for the ITT-Second Dose Recurrence Population. However, only a small portion of n=73 actually took a second dose of study drug for recurrence, i.e. 73/2851 [2.6%] of the ITT population receiving LTN in studies 301/302. Relative to those n=902 subjects being pain free at 2 hours, the portion of subjects choosing a second dose for recurrence is 73/902 [8.1%]. In view of the small number of affected patients it is evident that demonstration of statistically significant effects can hardly be achieved. Nonetheless, there were numerical advantages in favour of the second LTN dose observed in the pooled LTN/LTN group as compared to LTN/PBO across the main efficacy endpoints at the 2 hour post-dose time point (pain free: LTN/PBO 32.0%, LTN/LTN 50.0%; MBS free: LTN/PBO 40.9%, LTN/LTN 70.7%).

In essence, the favourable effect of the second dose of LTN taken for recurrence as compared to placebo is observed across all LTN doses (50, 100, 200 mg) and most meaningful endpoints (pain resp. MBS freedom 2 hours, pain relief). However, broken down to the single LTN doses, the number of affected subjects is so low that statistical significance could not be shown.

SmPC section 4.2 specifies that *no more than 200 mg should be taken in 24 hours,* i.e. that a second dose would not be eligible in those patients taking initially a 200 mg dose. Limitation of the MDD to 200 mg is derived from driving impairment studies where a significant impact on driving ability was found and only doses of up to 200 mg were tested. In consistency trial LAIJ, patients were not given the option of a second dose, thereby limiting the database. The benefit of the second dose taken for recurrence was only numerical, however, did not achieve statistical significance. In alignment with triptan posology an posology recommendations for administration of 2nd lasmiditan doses in case of recurrent pain has been introduced in SmPC section 4.2, taking due account on dose limitations (MDD of 200 mg) and time (2nd dose not to be taken within 2 hours after the initial dose).

Efficacy data for LTN second doses taken for rescue are less favourable. At the 2-hour post-dose assessment time point, the effect of the second LTN dose, taken for rescue, i.e. in those subjects not achieving pain freedom 2 hours after the first dose, numerically does not separate from placebo (LTN/PBO) across the pooled LTN dose groups (LTN/LTN). If the patient did not respond to the first dose of LTN, the second LTN dose taken for rescue is not considered to provide meaningful benefit in terms of pain resp. MBS freedom. Accordingly, SmPC section 4.2 proposed for LTN correctly specifies that *if*

the migraine attack has not resolved after taking a single LTN dose, a second dose has not been shown to be effective for the same attack.

Consistency of effect

In terms of consistency of effect, highly significant superiority over placebo could be shown for both LTN doses (100, 200 mg) in terms of the primary consistency endpoint in study LAIJ, pain freedom at 2 hours in 2 out of 3 attacks (placebo: 4.3%, L100 mg: 14.4%, L200 mg: 24.4%, ITT consistency population). Significant results were also obtained for pain relief and consistency across 2 out of 3 attacks in the subgroup of triptan insufficient responders (TIR).

The exploratory analysis of headache pain freedom in at least 3 out of 4 attacks adds further insight in the consistency of effect observed for LTN in study LAIJ. Differentiating between subgroups having experienced either 2, 3 or 4 attacks throughout the double blind treatment period, the rate of subjects not achieving pain freedom in any of these is around 18-23% across subgroups and LTN doses (100 mg, 200 mg). Hence, there was a group of around 20% of patients that could not successfully treat a single attack in multiple attack trial LAIJ. On the other side, a minority of 1.8% (L100 mg) resp. 2.9% (L200 mg) achieved pain freedom for each of the 4 attacks. A statistically significant higher portion of subjects achieved pain freedom in 3 out of 4 attacks (L100 mg: 7.4%, OR 3.01, p=0.004; L200 mg: 10.8%, OR 4.58, p<.001) as compared to control (2.6%). In general, treatment success was achieved more often in subjects receiving 200 mg as compared to 100 mg LTN. Overall, it is concluded that consistency of effect was adequately demonstrated in multiple attack trial LAIJ.

Supportive efficacy data are derived from open label long term study 305, which primarily recruited subjects taken over from studies 301/302. The overall portion of attacks that is successfully treated (i.e. achieved pain freedom at 2 hours post-dose) observed throughout 1-year treatment period (L100 mg: 26.7%, L200 mg: 32.2%) closely reproduces the portions achieved in the controlled single attack studies (301: L100 mg: 28.2%, L200 mg: 32.2%; 302: L100 mg: 31.4%, L200 mg: 38.8%). As can be expected given the overall discontinuation rate of 52.2%, the number of attacks treated per quarter decreases in the course of the trial, the portion of successfully treated attacks, however, does not (L100 mg: Q1: 27.3%, Q4: 29.6%; L200 mg: Q1: 32.7%, Q4: 31.2%).

At the start of long term study 305, patients were newly randomized to receive either 100 mg or 200 mg doses of LTN. A dose-response relationship is observed. The portions of 2-hours pain-free attacks are higher for the L200 mg dose arm as compared to L100 mg across all quarters.

Apart from analyses of attacks treated per quarter, it was also examined how treatment success evolves in patients with a large number of attacks suffered throughout the open label treatment course. Attacks were numbered as 1,2,3.. up to 20 relative to their order in a patient's history of treated attacks in study 305. For the treatment of up 20 attacks, the portion of successfully treated attacks (in terms of 2 hours pain freedom) only slightly decreases from attack 1 (36.6%) to attack 20 (31.5%) in the 200 mg LTN dose arm, while for the 100 mg LTN efficacy decreased more evidently from attack 1 (33.2%) to attack 20 (22.5%). The portions of treatment success in terms of 2 hours MBS freedom evolved in a similar way. However, the data should be interpreted with caution given the differences in the underlying database of treated attacks: attack 1 (L100 mg: N=969, L200 mg: N=983), attack 20 (L100 mg: N=120, L200 mg: L=111).

2.5.7. Conclusions on the clinical efficacy

The three pivotal randomized, placebo-controlled trials (301, 302, LAIJ) were designed concordant with IHS and EMA guidance and provide a sound database demonstrating evidence for the benefit of lasmiditan 50 mg, 100 mg, and 200 mg in acute migraine treatment across multiple measures of efficacy.

All 3 studies showed statistically significant effects on multiplicity-controlled analyses of their primary (pain freedom at 2 hours post-dose) and key secondary endpoints (MBS freedom at 2 hours post-dose) across all doses tested.

In study LAIJ, consistency of effect was shown across multiple attacks. Maintenance of effect was shown in open label study 305 providing supportive long-term data for intermittent use of LTN (100 mg, 200 mg) in acute migraine attacks over 1-year. Throughout the entire clinical programme response rates for the various endpoints generally increased with the lasmiditan dose.

One weakness of the overall database lies in the fact that the 50 mg dose arm was not included in study 301 and that no controlled data for consistency of effect (study LAIJ) resp. maintenance of effect (study 305) were provided for the LTN 50 mg dose. Available placebo-controlled efficacy data obtained from single attack study 302 and consistency study LAIJ (50 mg dose taken to treat the 3rd or 4th attack in subjects randomized to the control arm) demonstrate placebo superiority for the 50 mg dose and a dose response relationship across the 50 mg, 100 mg and 200 mg lasmiditan dose. It is therefore concluded that the B/R balance for the 50 mg strength is positive despite incompleteness of the underlying database. In the revised posology section of the SmPC it is specified that 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.

Given the chosen target population and baseline characteristics of included subjects, clinical data generated for lasmiditan are considered representative and transferable to the general episodic migraine population in clinical practice. Throughout all pivotal trials, patients were allocated to fixed LTN dose arms without the option to adapt the dose to the individual patient's need in the course of the study. This way, consistent superiority over placebo was shown across all dose arms (50, 100, 200 mg) in terms of most relevant efficacy measures. Hence, the clinical database does not fully elucidate which LTN dose should actually be chosen in LTN treatment initiation in clinical practice.

Based on available efficacy data, the proposed posology wording was endorsed in so far as indeed higher treatment success rates were observed with increasing doses.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Safety data from the oral Phase 2/3 studies were pooled.

Placebo-controlled Phase 2/3 Pool:	Intended to serve as the primary signal detection, safety evaluation to identify ADRs, and used for analyses of dose response.
All-Lasmiditan Pool:	Intended to identify any rare AEs or those that have a delayed onset.

Table 42: Safety Pools for EU Submission

Name of Integrated Analysis Set	Studies Included	Purpose	Doses/Attacks Included
Placebo-Controlled Phase 2/3 Pool Oral Placebo-Controlled Phase 2 and Phase 3 Studies All placebo-controlled first attacks	202/LAHO LAIH 301/LAHJ 302/LAHK LAIJ	• Primary signal detection • Safety evaluation to identify adverse drug reactions • Dose-response analyses	PBO All LTN doses combined and by dose group (as randomised). *Note: Does not include the 400 mg single dose from 202/LAHO.* LAIJ first attack only (does not include 50 mg)
All-Lasmiditan Pool All Lasmiditan-Treated Patients from Oral Phase 2 and Phase 3 Studies	202/LAHO LAIH 301/LAHJ 302/LAHK LAIJ-(DB) 305/LAHL LAIJ-(OLE)	• Identification of any rare adverse events or those that have a delayed onset	Descriptive only All LTN doses combined *Note: Includes the 400 mg single dose from 202/LAHO and 100 mg and 200 mg doses for multiple treated migraine attacks from Study 305/LAHL.* LAIJ all attacks (includes 50 mg; includes OLE)

Abbreviations: DB = double-blind; LTN = lasmiditan; OLE = open-label extension; PBO = placebo.

The Phase 2/3 Pool, used for the primary safety analyses, includes a total of 6922 patients (lasmiditan, n = 4861; placebo, n = 2061). There were a total of 2030 patients in the long-term open-label safety study (305/LAHL), and as of the data cut-off for this submission, there were 401 patients in Study LAIJ-OLE. The All-Lasmiditan Pool comprised 5916 lasmiditan-treated patients, which includes up to 4 attacks treated from the double-blind period of Study LAIJ, and long-term safety data from Studies 305/LAHL and LAIJ-OLE.

Table 43: Summary of Exposure in Safety Database for Lasmiditan, Phase 2 and Phase 3 Studies (201, 202, LAIH, 301, 302, LAIJ-DB, 305,LAIJ-OLE)

Clinical Trial Groups	Lasmiditan	Placebo
Controlled oral trials for migraine	4931	2061
Controlled intravenous trial for migraine	88	42
Uncontrolled (open-label) trial for migraine	2431	--
Placebo-controlled Phase 3 Studies	4148	1762
Oral Placebo-controlled Phase 2 and Phase 3 Studies (excluding 400mg group from 202/LAHO)	4861	2061
All Lasmiditan-treated from Oral Phase 2 and Phase 3 Studies*	5916	--

n = number of patients within each specific category.
*Patients in the open-label extension study are not counted twice unless they were in the placebo group in the controlled trials.

The following Table summarises the extent of exposure from the completed long-term open-label safety trial (Study 305/LAHL) and the number of patients who treated on average 2 or more migraine attacks per month for ≥3, ≥6, and ≥12 consecutive months.

Table 44: Number of Patients Exposed to Lasmiditan for Specified Numbers of Consecutive Months, Safety Population, Study 305/LAHL

		Number of Patients Exposed to Lasmiditan[a]		
		≥3 Months	≥6 Months	≥12 Months
LAHL	100 mg dose	383	184	98
	200 mg dose	348	181	88
	Total	731	365	186

[a] Note: Includes all patients who treated on average 2 or more migraine attacks per month in the time period of interest.

Adverse events

Overall, in the Phase 2/3 Pool, AEs were reported at a greater frequency in lasmiditan-treated patients (n = 2744, 57%) compared to placebo (n = 713, 33.5%). There were 2204 (45.7%) lasmiditan-treated patients and 358 (16.9%) patients taking placebo who reported TEAEs.

Time window for recording TEAE

Lasmiditan is a small molecule, orally administered on an intermittent, as-needed basis (that is, PRN) for the acute treatment of migraine attacks, with maximum serum concentrations achieved 1.8 hours following dose administration and a half-life of approximately 5.7 hours. For all clinical studies, a 48-hour window following dosing was used for identifying TEAEs.

Common TEAEs

Overall, as the lasmiditan dose increased, there were more patients in each dose group who reported at least 1 common TEAE (defined as an event occurring in ≥2% of patients in any LTN-treated dose group). The individual common TEAEs that met statistical significance in the test-of-trend for 100 mg and 200 mg treatment regimens were dizziness, paraesthesia, and nausea.

Table 45: Summary and Analysis of Common TEAEs by Dosing Group, Preferred Term by Decreasing Frequency 200 mg Group Safety Population, Placebo-Controlled Phase 2/3 Studies 202, LAIH, 301, 302, LAIJ

	PBO N=2061 n (adj%)	LTN 50 mg N=824 n (adj%)	LTN 100 mg N=2040 n (adj%)	LTN 200 mg N=1997 n (adj%)	P-value from Test of Trend
Patients with ≥1 TEAE	**358 (16.9)**	**265 (33.8)**	**923(45.0)**	**1016 (51.0)**	**<0.001**
Patients ≥1 Common TEAE	**195 (9.2)**	**197 (25.5)**	**730 (35.7)**	**844 (42.5)**	**<0.001**
Dizziness	68(3.2)	93 (12.2)	404 (19.9)	463(23.5)	0.009
Paraesthesia	30 (1.4)	19 (2.2)	121 (5.9)	166 (8.1)	0.003
Somnolence	47 (2.3)	50 (6.2)	139 (6.8)	161 (8.3)	0.131
Fatigue	20 (1.0)	29 (3.3)	111 (5.5)	118 (6.0)	0.521
Nausea	45 (2.1)	26 (3.3)	91 (4.4)	117 (5.6)	0.045
Asthenia	4 (0.2)	13 (2.0)	47(2.3)	62 (3.1)	0.117
Hypoaesthesia	7 (0.3)	4 (0.5)	50 (2.4)	58 (3.0)	0.372
Vertigo	4 (0.2)	14 (2.0)	52 (2.5)	58 (2.9)	0.488
Muscular weakness	2 (0.1)	11 (1.3)	48 (2.3)	52 (2.6)	0.608

Abbreviations: adj% = study size adjusted percentage; LTN = lasmiditan; N = number of patients in the analysis populations; n = number of patients within each specific category; PBO = placebo; TEAE = treatment-emergent adverse event.
Note: P-value from Test of Trend is from the Cochran-Armitage test for trend among the 2 dosing groups, LTN 100 mg and LTN 200 mg.

In the All-Lasmiditan Pool, common TEAEs (≥2%) reported in the lasmiditan-treated patients were dizziness (25%), somnolence (9.5%), paraesthesia (9.3%), fatigue (7.6%), nausea (6.8%), vertigo (3.9%), asthenia (3.3%), hypoaesthesia (2.9%), and muscular weakness (2.5%) (Table 2.7.4.13, not shown in detail). The proportion of lasmiditan-treated patients who reported ≥1 common TEAE was higher in the All-Lasmiditan Pool compared to the Phase 2/3 Pool. This finding is not surprising, as TEAEs in the All-Lasmiditan Pool include those from the long-term study 305/LAHL, up to 4 attacks from LAIJ-DB, and all attacks from LAIJ-OLE.

TEAEs by First Dose and Second Dose (Studies 301 and 302)

Among the Phase 2/3 Pool, only Studies 301 and 302 allowed for the option of a second dose of study drug for rescue or recurrence of migraine to be administered.

Table 46: Summary of Extent of Exposure By Number of Received Doses, Safety Population, Phase 3 Studies (301, 302)

Number of Received Doses	PBO/PBO (N=1262) n (%)	LTN 50mg/PBO (N=225) n (%)	LTN 50mg/LTN 50mg (N=429) n (%)	LTN 100mg/PBO (N=409) n (%)	LTN 100mg/LTN 100mg (N=856) n (%)	LTN 200mg/PBO (N=418) n (%)	LTN 200mg/LTN 200mg (N=840) n (%)	ALL LTN (N=3177) n (%)
One	500 (39.6)	129 (57.3)	223 (52.0)	240 (58.7)	476 (55.6)	265 (63.4)	537 (63.9)	1870 (58.9)
Two	762 (60.4)	96 (42.7)	206 (48.0)	169 (41.3)	380 (44.4)	153 (36.6)	303 (36.1)	1307 (41.1)

LTN = Lasmiditan; PBO = Placebo.

Of patients who took only 1 dose of study drug, there were more patients with at least 1 TEAE in the lasmiditan 200 mg (n = 291, 36.3%) and 100 mg (n = 230, 32.1%) dose groups compared with the 50 mg (n = 67, 19.0%) dose group.

Table 47: Summary of Common TEAEs in Patients Who Took Only 1 Dose, Safety Population, Placebo-Controlled Phase 3 Studies (Includes Patients Who Took Only One Dose; As Randomised), Studies 301, 302

	PBO/ PBO N=500 n(adj%)	**50 mg/ PBO** N=129 n(adj%)	**50 mg/ 50 mg** N=223 n(adj%)	**100 mg/ PBO** N=240 n(adj%)	**100 mg/ 100 mg** N=476 n(adj%)	**200 mg/ PBO** N=265 n(adj%)	**200 mg/ 200 mg** N=537 n(adj%)
Patients with ≥1 common TEAE	53 (10.6)	24 (18.6)	43 (19.3)	81 (33.8)	149 (31.2)	96 (36.2)	195 (36.3)
Dizziness	20 (0.4)	12 (9.3)	23 (10.3)	48 (20.0)	86 (18.1)	45 (17.0	103 (19.2)
Paraesthesia	6 (1.2)	3 (2.3)	4 (1.8)	15 (6.3)	34 (7.1)	28 (10.5)	41 (7.6)
Somnolence	19 (3.8)	10 (7.8)	14 (6.3)	14 (5.8)	26 (5.4)	15 (5.7)	44 (8.2)
Fatigue	3 (0.6)	3 (2.3)	7 (3.1)	15 (6.3)	20 (4.2)	16 (6.0)	24 (4.5)
Nausea	12 (2.4)	1 (0.8)	5 (2.2)	6 (2.5)	19 (4.0)	11 (4.1)	26 (4.8)
Hypoaesthesia	0 (0.0)	0 (0.0)	1 (0.4)	4 (1.7)	10 (2.1)	2 (0.7)	15 (2.8)
Muscular weakness	0 (0.0)	0 (0.0)	4 (1.8)	4 (1.7)	6 (1.3)	3 (1.1)	13 (2.4)
Vertigo	0 (0.0)	0 (0.0)	1 (0.4)	5 (2.1)	5 (1.1)	3 (1.1)	3 (0.6)
Vertigo CNS origin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)

Abbreviations: adj % = study size adjusted percentage; CNS = central nervous system; LTN = lasmiditan; N = number of patients in the analysis population; n = number of patients within each specific category; PBO = placebo; TEAE = treatment-emergent adverse event.

Note: The analyses of second dose were based only on Studies 301/LAHJ or 302/LAHK; in these studies, asthenia was not a common TEAE and so was not included in these analyses of first dose/second dose. The lasmiditan dose is shown in mg

In patients who took a second dose, the proportion of patients experiencing at least 1 common TEAE after the second dose was lower for all lasmiditan dose groups, compared with patients who took only 1 dose of study drug. This was true overall, and for each individual PT.

Table 48: Summary of Common TEAEs (after Second Dose), Safety Population, Placebo-Controlled Phase 3 Studies (Includes Only Patients Who Took a Second dose; As-Randomised), Studies 301, 302

	PBO/ PBO N=762 n(adj%)	50 mg/ PBO N=96 n(adj%)	50 mg/ 50 mg N=206 n(adj%)	100 mg/ PBO N=169 n(adj%)	100 mg/ 100 mg N=380 n(adj%)	200 mg/ PBO N=153 n(adj%)	200 mg/ 200 mg N=456 n(adj%)
Patients with ≥1 common TEAE	27 (3.5)	7 (7.3)	25 (12.1)	23 (13.5)	35 (9.2)	14 (9.2)	43 (14.2)
Dizziness	9 (1.2)	4 (4.2)	13 (6.2)	13 (7.7)	17 (4.5)	9 (5.9)	28 (9.2)
Paraesthesia	9 (1.2)	1 (1.0)	2 (1.0)	6 (3.5)	6 (1.6)	1 (0.7)	7 (2.3)
Fatigue	3 (0.4)	1 (1.0)	3 (1.5)	4 (2.3)	5 (1.3)	1 (0.7)	5 (1.6)
Nausea	4 (0.5)	2 (2.1)	4 (1.9)	4 (2.4)	5 (1.3)	2 (1.3)	2 (0.7)
Somnolence	3 (0.4)	0 (0.0)	4 (1.9)	2 (1.2)	8 (2.1)	1 (0.7)	3 (1.0)
Muscular Weakness	0 (0.0)	1 (1.0)	2 (1.0)	1 (0.6)	3 (0.8)	0 (0.0)	3 (1.0)
Hypoaesthesia	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	1 (0.3)
Vertigo	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo CNS origin	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: adj% = study size adjusted percentage; CNS = central nervous system; N = number of patients in the analysis population; n = number of patients within each specific category; PBO = placebo; TEAE = treatment-emergent adverse event.

Note: The analyses of second dose were based only on Studies 301/LAHJ or 302/LAHK; in these studies, asthenia was not a common TEAE and so was not included in these analyses of first dose/second dose.

Long-Term Safety from Open-Label Study LAHL

To understand the possible changes in the safety profile as the number of treated migraine attacks increased during the study, specific analyses were performed to determine event rates and event rate ratios from Study 305/LAHL.

TEAE per Migraine Attack and by Successive Treated Migraine Attacks from Study 305/LAHL

The incidence of common TEAEs by PT associated with migraine attacks 1 to 5, 10, 15, and 20 treated with lasmiditan was also analysed. Although the number of patients treating subsequent attacks decreased, the percentage of attacks associated with the TEAEs also decreased, in general, for each subsequent attack. For instance, in the lasmiditan 100 mg treatment group, 8.4% of first migraine attacks were associated with dizziness, but only 0.9% of the 15th migraine attacks treated were associated with dizziness.

Table 49: Summary of Common TEAEs, by Preferred Term and by Successive Migraine Attacks, Safety Population, Study 305

LTN 100 mg								
Preferred Term	1st Migraine N=991	2nd Migraine N=866	3rd Migraine N=759	4th Migraine N=674	5th Migraine N=615	10th Migraine N=368	15th Migraine N=226	20th Migraine N=147
Patients with ≥1 TEAE, n (%)	244 (24.6%)	134 (15.5%)	107 (14.1%)	74 (11.0%)	68 (11.1%)	26 (7.1%)	11 (4.9%)	9 (6.1%)
Dizziness	83 (8.4%)	48 (5.5%)	33 (4.3%)	24 (3.6%)	22 (3.6%)	5 (1.4%)	2 (0.9%)	3 (2.0%)
Somnolence	42 (4.2%)	27 (3.1%)	20 (2.6%)	6 (0.9%)	6 (1.0%)	6 (1.6%)	2 (0.9%)	0
Paraesthesia	31 (3.1%)	10 (1.2%)	12 (1.6%)	3 (0.4%)	2 (0.3%)	1 (0.3%)	0	0
Fatigue	26 (2.6%)	16 (1.8%)	13 (1.7%)	10 (1.5%)	5 (0.8%)	1 (0.3%)	1 (0.4%)	0
Nausea	15 (1.5%)	7 (0.8%)	3 (0.4%)	3 (0.4%)	0	1 (0.3%)	2 (0.9%)	0
Asthenia	8 (0.8%)	4 (0.5%)	4 (0.5%)	5 (0.7%)	4 (0.7%)	0	1 (0.4%)	0
Hypoaesthesia	9 (0.9%)	1 (0.1%)	0	1 (0.1%)	1 (0.2%)	0	0	0
Vertigo	5 (0.5%)	4 (0.5%)	2 (0.3%)	1 (0.1%)	1 (0.2%)	1 (0.3%)	1 (0.4%)	0
Lethargy	9 (0.9%)	3 (0.3%)	6 (0.8%)	3 (0.4%)	6 (1.0%)	1 (0.3%)	0	0
LTN 200 mg								
Preferred Term	1st Migraine N=1039	2nd Migraine N=915	3rd Migraine N=807	4th Migraine N=702	5th Migraine N=624	10th Migraine N=348	15th Migraine N=206	20th Migraine N=135
Patients with ≥1 TEAE, n (%)	339 (32.6%)	209 (22.8%)	152 (18.8%)	110 (15.7%)	88 (14.1%)	44 (12.6%)	20 (9.7%)	11 (8.1%)
Dizziness	124 (11.9%)	88 (9.6%)	63 (7.8%)	41 (5.8%)	28 (4.5%)	16 (4.6%)	7 (3.4%)	3 (2.2%)
Somnolence	66 (6.4%)	39 (4.3%)	19 (2.4%)	14 (2.0%)	11 (1.8%)	6 (1.7%)	3 (1.5%)	2 (1.5%)
Paraesthesia	55 (5.3%)	29 (3.2%)	21 (2.6%)	13 (1.9%)	17 (2.7%)	8 (2.3%)	6 (2.9%)	3 (2.2%)
Fatigue	37 (3.6%)	24 (2.6%)	13 (1.6%)	11 (1.6%)	7 (1.1%)	4 (1.1%)	2 (1.0%)	2 (1.5%)
Nausea	31 (3.0%)	13 (1.4%)	9 (1.1%)	6 (0.9%)	8 (1.3%)	1 (0.3%)	1 (0.5%)	0
Asthenia	14 (1.3%)	6 (0.7%)	5 (0.6%)	2 (0.3%)	3 (0.5%)	0	2 (1.0%)	0
Hypoaesthesia	14 (1.3%)	2 (0.2%)	4 (0.5%)	2 (0.3%)	3 (0.5%)	0	0	0
Vertigo	15 (1.4%)	5 (0.5%)	6 (0.7%)	7 (1.0%)	3 (0.5%)	2 (0.6%)	0	0
Lethargy	6 (0.6%)	7 (0.8%)	7 (0.9%)	5 (0.7%)	3 (0.5%)	0	0	0

Abbreviations: AE(s) = adverse event(s); LTN = lasmiditan; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients in treatment group; n = number of patients with a TEAE; TEAE(s) = treatment-emergent adverse event(s).

Note: An AE with the date/time of onset (or that worsened in intensity) at or within 48 hours after the time of dosing with study drug is considered treatment-emergent.

Percentages were calculated out of total (N) for each migraine subgroup.

AEs were coded using MedDRA Version 21.0.

Source: lillyce_(\\statclstr)_prd_ly573144_h8h_cd_lahl_ final_output_shared_tfl; Table 14.4.1.3.

Safety after Multiple Attacks in Placebo-Controlled Study LAIJ

Double-blind Phase (up to 4 doses)

A greater proportion of participants in the lasmiditan 100 mg and 200 mg treatment groups reported 1 or more TEAEs (67.6% and 72.2%) compared with placebo (32.4%). The 50 mg dose group from Study LAIJ had fewer TEAEs (17%) when compared to the 100 mg and 200 mg dose groups. (LAIJ CSR Table 5.29)

The common TEAEs observed in Study LAIJ were consistent with the types of events observed in the Phase 2/3 Pool (dizziness, paraesthesia, nausea, fatigue, somnolence, vertigo, asthenia, muscular weakness, hypoaesthesia).

In the by-attack analysis, the proportion of patients who reported 1 or more TEAEs was highest for the first treated migraine attack. The frequency of TEAEs was lower and similar across the second, third, and fourth treated migraine attacks. This pattern was observed in both the lasmiditan (100 mg and 200 mg) and placebo-treated patients. To adjust for confounding due to attrition, when the analysis was repeated for patients who treated 4 migraine attacks results were generally consistent with the analysis that included all participants in the safety population.

Table 50: Frequently Reported Treatment-Emergent Adverse Events by Individual Migraine Attack, Safety Population Double-Blind Period, Study LAIJ

Preferred Term, n (%)	First Treated Migraine N=485	Second Treated Migraine N=413	Third Treated Migraine N=329	Fourth Treated Migraine N=253
LTN 100 mg				
Participants with at least 1 TEAE	257 (53.0)	151 (36.6)	107 (32.5)	81 (32.0)
Dizziness	108 (22.3)	55 (13.3)	30 (9.1)	28 (11.1)
Paraesthesia	39 (8.0)	29 (7.0)	21 (6.4)	11 (4.3)
Nausea	31 (6.4)	15 (3.6)	7 (2.1)	13 (5.1)
Fatigue	37 (7.6)	16 (3.9)	11 (3.3)	9 (3.6)
Somnolence	20 (4.1)	16 (3.9)	8 (2.4)	3 (1.2)
Vertigo	24 (4.9)	16 (3.9)	15 (4.6)	11 (4.3)
Asthenia	14 (2.9)	8 (1.9)	3 (0.9)	6 (2.4)
Muscular weakness	16 (3.3)	11 (2.7)	3 (0.9)	2 (0.8)
LTN 200 mg				
Participants with at least 1 TEAE	297 (61.1)	190 (48.0)	123 (39.3)	80 (33.2)
Dizziness	129 (26.5)	81 (20.5)	63 (20.1)	40 (16.6)
Paraesthesia	62 (12.8)	49 (12.4)	29 (9.3)	21 (8.7)
Nausea	49 (10.1)	25 (6.3)	14 (4.5)	11 (4.6)
Fatigue	46 (9.5)	26 (6.6)	19 (6.1)	11 (4.6)
Somnolence	37 (7.6)	22 (5.6)	16 (5.1)	7 (2.9)
Vertigo	33 (6.8)	22 (5.6)	13 (4.2)	10 (4.1)
Asthenia	23 (4.7)	15 (3.8)	7 (2.2)	4 (1.7)
Muscular weakness	22 (4.5)	11 (2.8)	7 (2.2)	3 (1.2)
Placebo				
Preferred Term, n (%)	First Treated Migraine N=500	Second Treated Migraine N=438	Third or Fourth Treated Migraine N=317	
Participants with at least 1 TEAE	112 (22.4)	61 (13.9)	28 (8.8)	
Dizziness	23 (4.6)	8 (1.8)	8 (2.5)	
Paraesthesia	9 (1.8)	3 (0.7)	4 (1.3)	
Nausea	19 (3.8)	9 (2.1)	3 (0.9)	
Fatigue	9 (1.8)	4 (0.9)	2 (0.6)	
Somnolence	7 (1.4)	3 (0.7)	0	
Vertigo	1 (0.2)	3 (0.7)	0	
Asthenia	1 (0.2)	1 (0.2)	0	
Muscular weakness	2 (0.4)	0	1 (0.3)	

Abbreviations: LTN = lasmiditan; N = number of participants in the analysis population; n = number of participants with events meeting specified criteria; TEAE = treatment-emergent adverse event. Source: CSR Table LAIJ.5.33.

Serious adverse events and deaths

Deaths

There were no deaths in the safety population in the clinical trial database as of the cut-off date for this submission (12 June 2020).

Serious adverse events

In the Phase 2/3 Pool, there were 20 (0.4%) lasmiditan-treated patients and 6 (0.3%) placebo-treated patients that experienced at least 1 SAE (p=.388). There were 9 (0.2%) lasmiditan-treated patients and 2 (0.1%) placebo-treated patients that reported at least 1 TESAE (p=.424). Overall, there were no TESAE that occurred in more than one patient.

Table 51: Summary of Serious AEs By Decreasing Frequency in the Lasmiditan Group, Safety Population Oral Placebo-Controlled Phase 2/3 Studies 202, LAIH, 301, 302, LAIJ

	TESAE		non TESAE	
	PBO (N=2061)	All LTN (N=4861)	PBO (N=2061)	All LTN (N=4861)
Preferred Term	n (%) [adj %]	n (%) [adj %]	n (%) [adj %]	n (%) [adj %]
Patients with at least one event	2 (0.1) [0.1]	9 (0.2) [0.2]	4 (0.2) [0.2]	11 (0.2) [0.2]
Asthma	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Dizziness	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Hemiplegic migraine	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Hypertension	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Hypotension	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Pituitary tumour benign	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Presyncope	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Serotonin syndrome	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Surgery	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Abscess oral	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Appendicitis	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Bronchitis	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Cholelithiasis	1 (0.0) [0.1]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Deep vein thrombosis	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Endometriosis*b	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.1) [0.1]	0 (0.0) [0.0]
Haemorrhoids thrombosed	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Hand fracture	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Headache	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]
Intestinal obstruction	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.1]	0 (0.0) [0.0]
Lower limb fracture	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Lung adenocarcinoma	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]
Menorrhagia*b	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Metrorrhagia*b	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Non-cardiac chest pain	1 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]
Somatic symptom disorder	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Tracheal mass	0 (0.0) [0.0]	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]
Vomiting	0 (0.0) [0.0]	0 (0.0) [0.0]	1 (0.0) [0.0]	0 (0.0) [0.0]

LTN = Lasmiditan; PBO = Placebo; TESAE = Treatment-Emergent Serious Adverse Event.
LAIJ refers to first attack data from Study LAIJ.
Treatment-Emergent Serious Adverse Events refer to serious adverse events occurring within 48 hours after first dose, regardless of whether a second dose was taken.
N = number of patients in the analysis population; n = number of patients within each specific category.
*a - denominator adjusted for male-specific event;
*b - denominator adjusted for female-specific event.
MedDRA version 23.0.

In the All-Lasmiditan Pool, a total of 95 patients reported 1 or more SAEs (Table 2.7.4.16). A total of 22 lasmiditan-treated patients experienced a TESAE, 13 additional to those described in the Phase 2/3 Pool. In the All-Lasmiditan Pool no further TESAE of dizziness or serotonin syndrome was observed. Among those SAE occurring additionally to those already discussed for the Phase 2/3 Pool are cellulitis, diverticulitis, gastritis, limb abscess, bradycardia, carbuncle, acute cholecystitis, endometriosis, lumbar spinal stenosis, nephrolithiasis, sinus node dysfunction, sinusitis, and recurrent thyroid cancer. With regard to a potential relatedness to lasmiditan, particular attention is paid to the SAE of bradycardia.

Laboratory findings

There were no significant differences observed in either mean changes or categorical shifts between baseline and post-baseline values for blood chemistry, haematology, or urinalysis between lasmiditan- and placebo-treated patients. As limitations, laboratory parameters in the clinical trials were not necessarily assessed in temporal proximity to dosing of lasmiditan and were not collected in fasting conditions. Analysis of the subgroup of patients that had laboratory assessments in the treatment-emergent period did not suggest any meaningful changes.

Safety in special populations

Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs and quantitative ECG parameters remained stable throughout the placebo-controlled Phase 2/3 Pool. Both treatment groups had small mean changes and categorical shifts in vital signs and ECG parameters that were not statistically different and not found to be clinically meaningful. No appreciable

changes were noted in the All-Lasmiditan Pool as well. Given that in all Phase 2 and 3 studies of orally administered lasmiditan, vital signs and ECG measurements were not necessarily assessed in temporal proximity to dosing of lasmiditan, interpretation of any changes observed, and their clinical relevance is limited. Analysis of the subgroup of patients that had vital sign or ECG measurements during the 48 hours after dosing were consistent and did not suggest any meaningful changes.

Assessments during the 48-hour period after dosing with study drug

There were 200 lasmiditan-treated patients and 64 placebo-treated patients in the Phase 2/3 Pool who had vital sign assessments performed during the 48 hours after dosing. The lasmiditan- and placebo-treated patients were similar in their mean and median observed values for baseline and post-baseline SBP, DBP, and pulse.

Table 52: Summary Statistics of SBP, DBP, and Heart Rate for Patients Assessed in Treatment-Emergent Period, Safety Population, Oral Placebo-Controlled Phase 2 / 3 Studies 202, LAIH, 301, 302

Parameter	SBP (mm Hg)		DBP (mm Hg)		Pulse (bpm)	
	All LTN	PBO	All LTN	PBO	All LTN	PBO
Baseline (mean)	121.10	120.98	78.50	78.64	74.42	70.41
Postbaseline (mean)	119.88	120.16	77.78	77.19	77.31	73.73
Mean changes	-1.22	-0.83	-0.73	-1.45	2.90	3.33

Abbreviations: DBP = diastolic blood pressure; LTN = lasmiditan; PBO = placebo; SBP = systolic blood pressure; TE = treatment-emergent.

Note: There were no patients with TE vital sign assessments from Study LAIH.

In all Phase 2/3 Studies vital signs resp. ECG parameters were not necessarily assessed in temporal proximity to dosing of lasmiditan. However, in clinical pharmacology studies (LAHU, LAHD, LAIG) where measurement of vital signs was done at regular intervals after dosing, the findings were more pertinent.

Vital signs in Clinical Pharmacology Studies

Two studies assessed BP using 24-hour ambulatory BP monitoring (ABPM):

- Study **LAHU** (4-period, LTN 200 mg, sumatriptan 100 mg, administered either alone or together) in non-elderly subjects
- Study **LAIG** (3-period, CV effects of LTN 100 mg, LTN 200 mg) in elderly subjects

Study LAHU assessed the effect of lasmiditan 200 mg and placebo on SBP and DBP using ambulatory BP monitoring for up to 24 hours post-dose.

Table 53: Study LAHU Ambulatory Blood Pressure Monitoring in Non-Elderly Subjects

	SBP change from baseline vs pbo (mm Hg)	90% CI for the difference (Lower, Upper)	DBP change from baseline vs pbo (mm Hg)	90% CI for the difference (Lower, Upper)
Time-post dose (h)	200 mg LTN	200 mg LTN	200 mg LTN	200 mg LTN
1	2.65	(-0.46, 5.77)	0.95	(-1.59, 3.49)
2	-1.85	(-4.97, 1.26)	-3.66	(-6.20, -1.12)
3	-3.22	(-6.34, -0.10)	-5.85	(-8.38, -3.31)
4	-0.86	(-3.98, 2.25)	-3.27	(-5.81, -0.73)
5	-2.06	(-5.18, 1.06)	-4.65	(-7.19, -2.11)
6	-2.31	(-5.43, 0.81)	-3.67	(-6.21, -1.13)
7	-1.84	(-4.95, 1.28)	-2.00	(-4.53, 0.54)
8	-1.08	(-4.22, 2.05)	-1.53	(-4.08, 1.03)
9	-0.83	(-3.97, 2.31)	-2.16	(-4.71, 0.40)
10	1.09	(-2.07, 4.25)	-2.78	(-5.35, -0.20)
11	0.73	(-2.43, 3.89)	-0.34	(-2.91, 2.23)
12	-0.12	(-3.24, 3.00)	-0.65	(-3.18, 1.89)
13	0.41	(-2.71, 3.53)	-1.83	(-4.36, 0.71)
14	-0.52	(-3.66, 2.61)	-3.63	(-6.18, -1.07)
15	2.01	(-1.15, 5.17)	-0.05	(-2.63, 2.52)
16	2.20	(-0.95, 5.36)	1.91	(-0.66, 4.49)
17	1.84	(-1.34, 5.02)	1.08	(-1.51, 3.67)
18	4.75	(1.59, 7.90)	3.22	(0.65, 5.79)
19	2.66	(-0.50, 5.82)	1.81	(-0.77, 4.38)
20	2.81	(-0.35, 5.97)	1.32	(-1.25, 3.89)
21	1.07	(-2.06, 4.21)	0.26	(-2.29, 2.81)
22	1.76	(-1.38, 4.89)	1.37	(-1.19, 3.92)
23	0.42	(-2.72, 3.55)	0.31	(-2.24, 2.87)
24	2.15	(-0.98, 5.29)	1.13	(-1.43, 3.68)

Abbreviations: CI = confidence interval; DBP = diastolic blood pressure; h = hour(s); LTN = lasmiditan; pbo = placebo; SBP = systolic blood pressure.

Study LAIG was conducted in elderly healthy volunteers and included assessment of SBP and DBP by ambulatory blood pressure monitoring (ABPM) over a period of 24 hours post-dose following administration of lasmiditan 100 mg, 200 mg, or placebo.

Following administration of lasmiditan 100 mg, lasmiditan 200 mg, or placebo, mean increases in SBP were observed up to 4 hours post-dose, with maximum increases of 9.7 mm Hg (1 to 2 hours post-dose), 6.6 mm Hg (1 to 2 hours post-dose), and 7.3 mm Hg (3 to 4 hours post-dose).

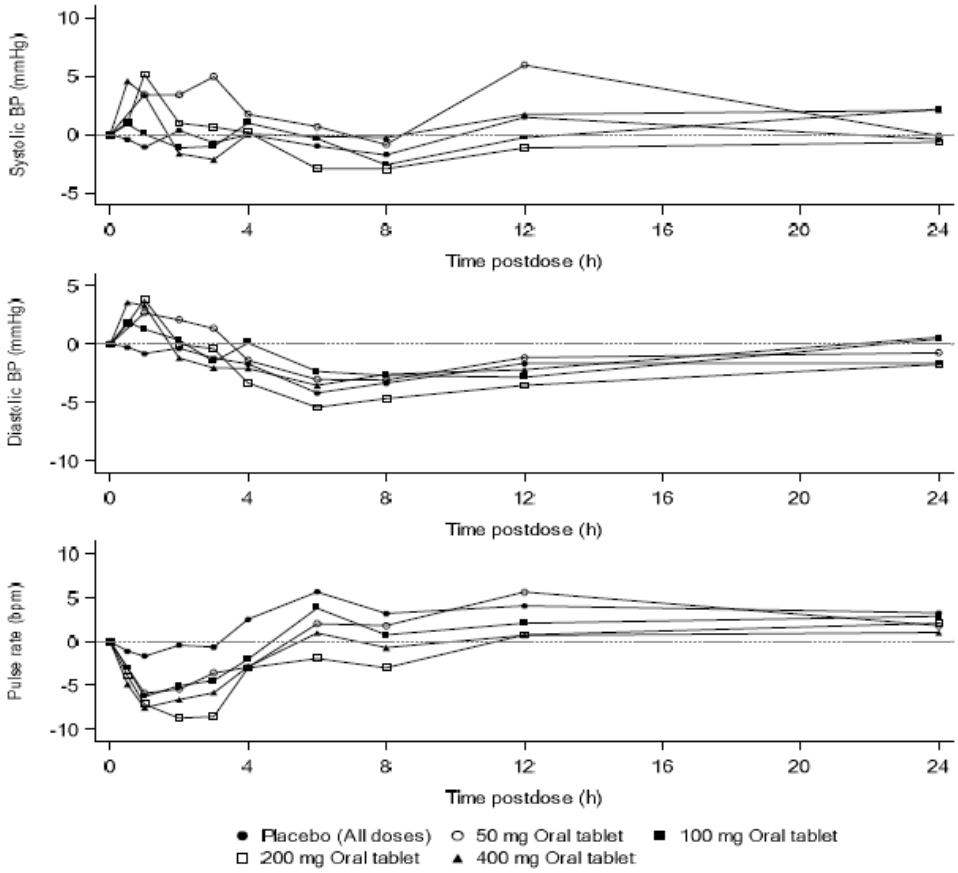
Table 54: Study LAIG Ambulatory Blood Pressure Monitoring in Elderly Subjects

	SBP change from baseline vs pbo (mm Hg)				DBP change from baseline vs pbo (mm Hg)			
Time-post dose (h)	100 mg LTN	95% CI for the difference (Lower, Upper)	200 mg LTN	95% CI for the difference (Lower, Upper)	100 mg LTN	95% CI for the difference (Lower, Upper)	200 mg LTN	95% CI for the difference (Lower, Upper)
1	5.38	(0.99, 9.77)	3.75	(-0.58, 8.08)	0.09	(-3.13, 3.31)	-0.23	(-3.41, 2.95)
2	2.36	(-2.03, 6.75)	-2.47	(-6.79, 1.86)	-1.73	(-4.96, 1.49)	-4.27	(-7.45, -1.09)
3	-0.51	(-4.90, 3.87)	-4.10	(-8.43, 0.22)	-4.24	(-7.46, -1.01)	-6.24	(-9.42, -3.06)
4	-3.33	(-7.72, 1.06)	-4.62	(-8.94, -0.29)	-3.13	(-6.35, 0.10)	-3.62	(-6.80, -0.44)
5	-3.16	(-7.55, 1.23)	-6.31	(-10.64, -1.99)	-6.07	(-9.30, -2.85)	-6.10	(-9.28, -2.92)
6	-3.72	(-8.11, 0.67)	-4.75	(-9.10, -0.39)	-4.27	(-7.49, -1.05)	-3.46	(-6.66, -0.26)
7	-2.84	(-7.23, 1.54)	-0.82	(-5.15, 3.51)	-1.94	(-5.17, 1.28)	-1.71	(-4.89, 1.47)
8	-3.96	(-8.35, 0.43)	-3.28	(-7.63, 1.08)	-4.41	(-7.63, -1.19)	-5.00	(-8.20, -1.80)
9	-1.95	(-6.34, 2.44)	-2.42	(-6.78, 1.93)	-1.55	(-4.77, 1.67)	-2.34	(-5.55, 0.86)
10	-4.24	(-8.63, 0.15)	-4.62	(-8.98, -0.26)	-2.27	(-5.50, 0.95)	-4.51	(-7.72, -1.31)
11	-3.35	(-7.77, 1.07)	-3.49	(-7.88, 0.90)	-4.10	(-7.35, -0.86)	-5.18	(-8.40, -1.95)
12	-3.52	(-7.94, 0.89)	-6.16	(-10.55, -1.77)	-1.82	(-5.07, 1.42)	-4.33	(-7.55, -1.10)
13	-3.80	(-8.22, 0.62)	-6.45	(-10.87, -2.02)	-2.44	(-5.68, 0.81)	-4.74	(-7.99, -1.49)
14	-1.07	(-5.49, 3.35)	-4.16	(-8.55, 0.23)	-2.17	(-5.42, 1.07)	-3.10	(-6.32, 0.13)
15	-1.57	(-6.02, 2.89)	-0.96	(-5.39, 3.46)	-2.09	(-5.36, 1.18)	-1.64	(-4.89, 1.61)
16	-2.57	(-7.03, 1.88)	-2.35	(-6.74, 2.04)	-1.30	(-4.57, 1.97)	-1.29	(-4.51, 1.94)
17	-2.02	(-6.47, 2.44)	0.12	(-4.27, 4.51)	0.33	(-2.94, 3.60)	1.12	(-2.11, 4.34)
18	-0.19	(-4.60, 4.23)	-0.81	(-5.24, 3.61)	1.42	(-1.82, 4.67)	0.56	(-2.69, 3.81)
19	0.43	(-3.99, 4.85)	0.34	(-4.05, 4.73)	0.94	(-2.31, 4.18)	0.81	(-2.42, 4.03)
20	-1.79	(-6.24, 2.66)	-1.05	(-5.48, 3.37)	0.46	(-2.81, 3.73)	-0.49	(-3.74, 2.76)
21	-3.26	(-7.68, 1.16)	-1.60	(-5.99, 2.79)	-2.75	(-5.99, 0.50)	-2.59	(-5.82, 0.64)
22	-0.81	(-5.27, 3.64)	-2.53	(-6.93, 1.86)	-0.79	(-4.06, 2.48)	-1.19	(-4.42, 2.03)
23	0.11	(-4.31, 4.53)	-0.75	(-5.18, 3.67)	0.64	(-2.60, 3.89)	0.00	(-3.25, 3.25)
24	-0.18	(-4.67, 4.30)	0.54	(-4.03, 5.10)	-0.86	(-4.15, 2.43)	-0.24	(-3.59, 3.12)

Abbreviations: CI = confidence interval; DBP = diastolic blood pressure; h = hour(s); LTN = lasmiditan; pbo = placebo; SBP = systolic blood pressure.

The mean changes in vital signs (SBP, DBP, pulse) were calculated based on the results of 16 clinical pharmacology studies (data generated either by repetitive BP measuring or ABPM).

Figure 12: Change from baseline vital signs in nonelderly healthy volunteers following single dosing with placebo or lasmiditan in the clinical pharmacology studies.



Baseline day as specified per SAP for each individual study
Non-elderly healthy volunteers, single dose studies: 102/LAHS, 103/LAHQ, 104/LAHR, 105/LAHP, 106/LAHG, 110/LAHH, 113/LAHN, 114/LAHF, 118/LAHI, LACA, LAHA, LAHD, LAHE, LAHT, LAHU, LAIF

Key Abuse Liability (AL) TEAEs by Dose Response as Randomised

There were numerical increases in key AL TEAEs with increasing LTN dose, in particular for Feeling abnormal (PBO: n=1, L50 mg: n=3, L100 mg: n=25, L200 mg: n=26) and to a lesser extent for Euphoric mood, abnormal dreams, and Feeling drunk.

Table 55: Summary and Analysis of Key Abuse Liability TEAEs by Dosing Group as Randomised, Safety Population Placebo-Controlled Phase 2/3 Studies 202, LAIH, 301, 302, LAIJ

	PBO N=2061 n (adj%)	LTN 50 mg N=824 n (adj%)	LTN 100 mg N=2040 n (adj%)	LTN 200 mg N=1997 n (adj%)	P-value from Test of Trend
Feeling abnormal	1 (0.1)	3 (0.4)	25 (1.2)	26 (1.3)	0.828
Euphoric mood	1 (0.0)	3 (0.3)	9 (0.5)	6 (0.3)	0.462
Abnormal dreams	1 (0.0)	1 (0.1)	7 (0.3)	4 (0.2)	0.384
Feeling drunk	0 (0.0)	0 (0.0)	3 (0.1)	3 (0.1)	0.979
Mental impairment	0 (0.0)	0 (0.0)	1 (0.0)	2 (0.1)	0.551
Dysphoria	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0.312
Apathy	1 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	0.312
Hallucination	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0.988
Hallucination, visual	0 (0.0)	0 (0.0)	2 (0.1)	7 (0.4)	0.089
Hallucination, auditory	--	--	--	--	--
Depersonalisation/derealisation disorder	0 (0.0)	0 (0.0)	2 (0.1)	1 (0.0)	0.576
Illusion	--	--	--	--	--

Abbreviations: adj% = study size adjusted percentage; LTN = lasmiditan; N = number of patients in the analysis population; n = number of patients within each specific category PBO = placebo.
Note: P-value from Test of Trend is from the Cochran-Armitage test for trend among the 2 dosing groups, LTN 100 mg and LTN 200 mg.

Cardiovascular Safety – Safety Topic of Interest

Migraine is an independent risk factor for CVD (Hippisley-Cox et al. 2017; Mahmoud et al. 2018). In addition, migraine is associated with an increased risk of a number of CV events, which are associated with increased morbidity. Migraine populations have shown increased relative risks (RRs) for CV events including ischemic stroke, transient ischemic attack, ischemic heart disease, and myocardial infarction compared with non-migraine populations (Kurth et al. 2006; Becker et al. 2007; Sacco et al. 2015; Peng et al. 2017; Adelborg et al. 2018).

In the Phase 2/3 Pool, baseline CVD was reported in 16.3% of lasmiditan-treated patients and in 16.9% of placebo-treated patients.

The SMQ with the highest frequency in the CVD "yes" subgroup for the Phase 2/3 Pool (lasmiditan vs placebo) was the Hypertension SMQ (n = 642, 13.1% vs n = 280, 13.8%). The CVD noted at baseline (by SMQ) included 63 patients with Ischemic Heart Disease, 136 patients with Cardiac arrhythmia, 30 patients with Cardiomyopathy, and 48 patients with Ischemic CNS vascular conditions when combined in the treatment groups.

The most frequent CV PTs reported were hypertension (n = 610, 12.5% vs n = 263, 13.0 %), angina pectoris (n = 17, 0.3% vs n = 8, 0.5%), deep vein thrombosis (n = 15, 0.3% vs n = 8, 0.4%), myocardial infarction (n = 14, 0.3% vs n = 4, 0.2%), transient ischaemic attack (n = 12, 0.2% vs n = 6, 0.3%), pulmonary embolism (n =12, 0.2% vs n = 9, 0.4%), blood pressure increased (n=11, 0.2% vs n=4, 0.2%), and CAD (n = 9, 0.2% vs n = 7, 0.4%).

Likely CV Treatment-Emergent Adverse Events - Placebo-Controlled Phase 2/3 Pool

The number and percentage of patients with at least 1 likely CV TEAE was statistically significantly higher in those treated with lasmiditan (n = 77, 1.6%) than those treated with placebo (n = 13, 0.6%).

The Cardiac arrhythmias SMQ had the highest frequency of likely CV TEAEs that were also statistically significantly higher in lasmiditan-treated patients compared with placebo-treated patients (n = 65, 1.4%

vs n = 11, 0.5%). This was primarily due to events of palpitations (n = 41, 0.9% vs n = 8, 0.4%), tachycardia (n = 9, 0.2% vs n = 0, 0.0%), and heart rate increased (n = 8, 0.2% vs n = 2, 0.1%).

Hepatic Safety

Abnormal Hepatic Laboratory Measures -All-Lasmiditan Pool

The frequency of ALT elevations ≥3xULN and ≥5xULN was 0.6% and 0.1%, respectively. In patients with normal baseline measurements, ALT elevations ≥3xULN and ≥5xULN were 0.2% and <0.1%, respectively. One patient reported an ALT elevation of ≥10xULN; this patient had a baseline ALT of >1xULN and <3xULN. Two patients (0.2%) had the abnormal laboratory results during the treatment-emergent period, both levels ≥3xULN.

The frequency of AST elevations ≥3xULN, ≥5xULN, and ≥10xULN was 0.3%, 0.1%, and 0.1%, respectively. Of these, the abnormal laboratory results occurred in the treatment-emergent period for 2 patients (1 patient each in ≥5xULN and ≥10xULN).

Four patients (0.1%) experienced ALP elevations of ≥2xULN, 2 of which had normal baseline measurements. Two occurred during the treatment-emergent period, but the patients had baseline levels ≥1.5xULN.

Two patients experienced a TBL ≥2xULN in the All-Lasmiditan Group, 1 of who had elevated levels at baseline. Neither were reported in the treatment-emergent period.

Reference lines are included to determine various states and includes the following:

- Hyperbilirubinemia: TBL at least 2xULN and ALT <3xULN
- Normal Range: TBL ≤1xULN and ALT ≤1xULN
- Temple's Corollary: TBL ≤1xULN and ALT at least 3xULN
- Biochemical indication of Hy's Law: TBL at least 2xULN and ALT at least 3xULN

Hy's law is defined as the combination of criteria: drug-related elevation of ALT ≥3xULN and TBL ≥2xULN, in the absence of significant cholestasis (that is, ALP <2xULN), and in the absence of other causes of liver injury.

One patient had a maximum AST ≥3xULN and maximum TBL ≥2xULN:

- The patient experienced hepatic laboratory abnormalities of AST ≥3xULN and TBL ≥2xULN, 10 days after their most recent dose of study drug. They had previously participated in Study 301/LAHJ, in which they were randomised to placebo/placebo. On the date of randomization in Study 301/LAHJ, their ALT, AST, TBL, and ALP were all within normal limits. On the final visit of Study 301/LAHJ and the initial visit for Study 305/LAHL, the patient's ALT and AST were both within normal limits, but TBL was elevated at 26 µmol/L (ULN 21 µmol/L). At Visit 2 29 days after randomization, the patient's AST was elevated, meeting ≥3xULN criteria, and measuring 161 U/L (ULN 37 U/L). Bilirubin was also elevated meeting ≥2xULN criteria, measuring 43 U/L, and ALT was high, measuring 107 U/L (ULN 41 U/L). The patient had reported currently smoking in Study 301/LAHJ and taking acetylsalicylic acid for cardiac prophylaxis since 2008. Additional medical history included drug hypersensitivity (penicillin), tension headache, and insomnia. They treated a total of 7 migraine attacks during Study 305/LAHL, taking 2 doses for each attack. Repeat laboratory tests were performed 43 days after randomization, which showed an ALT of 71 U/L, AST of 48 U/L, TBL of 12 µmol/L, and ALP of 89 U/L. The patient was discontinued 101 days after randomization due to withdrawal by subject ("pt wishes to participate in other trials"). On this same date, 17 days after the last dose of lasmiditan, their laboratory values were as follows: ALT 69 U/L, AST 91 U/L, TBL 40 µmol/L, and ALP 88 U/L. The investigator did not report

the hepatic laboratory abnormalities as AEs, and therefore, no assessment of relatedness was provided.

Suicidal Ideation or Behaviour and Non-suicidal Self-Injurious Behaviour as a Safety Topic of Interest

Suicidal ideation and behaviour is an important safety topic of interest because patients with migraine are deemed to be at a greater risk for suicidality (Breslau et al. 2012). Suicidal ideation and behaviour was assessed in all Phase 3 clinical trials (and Study LAIH) using the C-SSRS (Posner et al. 2011).

C-SSRS Affirmative Responses - Placebo-Controlled Phase 2/3 Pool

In the Phase 2/3 Pool, there were a total of 6 patients who had a positive response post-baseline. Of these, 6 (4 lasmiditan-treated patients and 2 placebo-treated patients) reported an affirmative response (or responses) to any question of the C-SSRS at a follow-up visit that had been answered with a negative response (or responses) at baseline.

C-SSRS Affirmative Responses - All-Lasmiditan Pool

In the All-Lasmiditan Pool, a total of 37 patients responded affirmatively to any item on the CSSRS at any time post-baseline. Of those, a total of 34 patients (0.6%) responded affirmatively to items reflecting suicidal ideation at any time post-baseline and 5 patients (0.1%) responded affirmatively to items reflecting suicidal behaviour at any time post-baseline. One patient responded affirmatively to the item on the C-SSRS capturing self-injurious behaviour without suicidal intent.

Serotonin Syndrome

The suspicion of serotonin syndrome in a patient receiving a serotonergic agent is usually guided by the triad of neuromuscular excitation (including the hallmark sign of clonus), autonomic excitation (for example, diaphoresis, hyperthermia, tachycardia), and altered mental status (for example, confusion, hypomania, agitation). The diagnosis is based on clinical signs and symptoms, after exclusion of other potential causes. The 2 validated sets of diagnostic criteria are the Hunter Serotonin Toxicity Criteria (Dunkley et al. 2003) and Sternbach Criteria (Sternbach 1991), with the former being more sensitive and specific.

The Applicant conducted a medical review, and cases which preliminarily appeared that they might meet the Hunter or Sternbach criteria were then thoroughly evaluated for information including associated AEs, timing of AEs, severity, seriousness, concomitant medications, and medical history. This analysis was done for all of the individual phase 2 and phase 3 studies with lasmiditan.

Fifteen cases (2 serious and 13 nonserious) in patients exposed to lasmiditan were identified via the search strategy, which on initial review of PTs warranted further evaluation. After further review of the 15 cases, one met Hunter Criteria and Sternbach criteria, 2 patients possibly met Sternbach criteria and 3 additionally were reported with the PT of serotonin syndrome.

Overall, for these 6 cases, 3 were from Phase 3 Study LAIJ (one of which was reported after the database lock for the study but included here for completeness), and 1 each from Phase 2 Study 201/LAHM (IV administration), Phase 2 Study 202/LAHO, and Phase 3 Study 305/LAHL.

All 6 were female, with ages ranging from 23 to 61 years of age (average age 44). Of the 6 cases, 4 cases were reported as non-serious, 2 of them as medically serious although 1 required no intervention and 1 case was serious for hospitalisation requiring active treatment. Two cases had confirmed use of other serotonergic agents, though details of the exact timing of these with respect to lasmiditan exposure were not available. Three of the patients discontinued from the studies due to the reported events, and all events were recovered/resolved.

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

In vivo DDI studies were conducted with sumatriptan (studies 118/LAHI, LAHU), propranolol (study LAHD) and topiramate (study LAHT).

In studies LAHU and LAHT, there were no clinically significant changes in ECG, clinical laboratory parameters, or vital signs when a single dose of lasmiditan or placebo was co-administered with sumatriptan or topiramate (as compared to when given the respective agents alone).

Study LAHD therefore assessed the safety of single doses of lasmiditan 200 mg with propranolol 80 mg BID with Holter ambulatory monitoring and vital signs.

During the 12 hours following co-administration of lasmiditan and propranolol, mean decreases from baseline in supine pulse rate were observed, ranging from 6.6 to 19.3 bpm. The greatest decrease of 19.3 bpm was noted at 1.5 hours post-dose for combined administration, compared with maximum decreases from baseline of 10.7 bpm and 14.2 bpm following dosing with lasmiditan or propranolol alone, respectively. Thus, the difference between the greatest decreases in mean supine pulse rate following administration of propranolol alone and co-administration of lasmiditan and propranolol was 5.1 bpm.

For a more detailed discussion of studies LAHU and LAHD, please refer to section 3.3.2.

Concomitant intake of lasmitditan and sumatriptan cannot not be excluded. The drug-related TEAEs of the SOC "Nervous system" in studies LAHI and LAHU assessing interactions between lasmiditan and sumatriptan were presented. Comparisons of TEAE of the SOC "Nervous system" did not show meaningful difference between lasmiditan alone and lasmiditan with sumatriptan group. However, given the limited sample size (N=40), and the mechanism of action of the two drugs, sumatriptan as selective agonist of 5HT1B and 5HT1D receptors, and lasmiditan as selective agonist of 5HT1F receptors, potentiation in case of concomitant administration of the two drugs cannot be excluded. Therefore, TEAE of the SOC "Nervous system" in such co-administration should be followed-up as part of the first PSUR.

Discontinuation due to AES

In the Phase 2/3 Pool, the proportion of patients who discontinued due to an AE was significantly greater in lasmiditan-treated patients (n = 44, 1.0%) than placebo-treated patients (n = 3, 0.1%) ($p \leq .001$). There were 37 (0.8%) lasmiditan-treated patients and 1 placebo-treated patient that discontinued due to TEAE. For an individual AE, discontinuation due to dizziness was the only one that was statistically significantly higher in the lasmiditan-treated patients (p=.010). The events that led to discontinuation in more than 1 lasmiditan-treated patient included dizziness (n = 13), vertigo (n = 4), fatigue (n = 3), nausea (n = 3), feeling abnormal (n = 2), and restlessness (n = 2). There was 1 (0%) DCAE due to SAE.

There were more discontinuations due to AEs in the All-Lasmiditan Pool compared with the Phase 2/3 Pool. This was expected because this pool included the long-term studies 305, LAIJ-OLE and all 4 attacks from the LAIJ double-blind phase, thus providing more dosing opportunities. In the All-Lasmiditan Pool, 351 (5.9%) patients discontinued due to an AE (2.7.4.18), the majority due to dizziness (n = 99, 1.7%), paraesthesia (n = 29, 0.5%), fatigue (n = 27, 0.5%), somnolence (n = 27, 0.5%), nausea (n = 23, 0.4%), vertigo (n = 17, 0.3), hypoaesthesia (n = 11, 0.2%), and asthenia (n = 9, 0.2%). Fifteen patients discontinued due to the AE of pregnancy.

Post marketing experience

Lasmiditan was first approved in the US (first global approval) on 11 October 2019 by the FDA.

Post-Marketing Exposure

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. It should also be noted that early sales of a newly marketed product may often reflect stocking by wholesalers as opposed to actual consumption by patients.

Due to the low number of cases, as well as insufficient information in most of the cases, comparison to background rate is not appropriate at this time.

2.5.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

A sound and comprehensive analysis of clinical trial data was provided to characterize the safety profile of lasmiditan as an acute treatment for migraine attacks. The primary safety analyses are based on 6 studies, 5 of which were randomised, placebo-controlled, double-blind and 1 long-term, open-label study. They were grouped into the Placebo-controlled Phase 2/3 Pool (dose finding study 202, single attack studies 301 / 302, Japanese study LAIH, consistency trial LAIJ for the first attack) and the All-Lasmiditan Pool, additionally comprising all multiple attacks of LAIJ, long-term open-label study 305 and open-label extension (OLE) of LAIJ.

Exposure

In terms of overall exposure, the Phase 2/3 Pool, used for the primary safety analyses, includes a total of 6922 patients (lasmiditan, n = 4861; placebo, n = 2061). There were a total of 2030 patients in the long-term open-label safety study (305/LAHL), and as of the data cut-off for this submission, there were 401 patients in Study LAIJ-OLE. The All-Lasmiditan Pool comprised 5916 lasmiditan-treated patients. The minimum requirements for long term exposure over $\geq$6 (N=365) resp. 12 months (N=186) according to ICH E1 are met.

Demographics

Around 3.5% of the safety population was older than 65 years old. Patients with a history of cardiovascular disease were not excluded. A portion of 16.3% (All LTN) of subjects presented with relevant baseline cardiovascular disease. The CVD that was reported most often is hypertension SMQ (N=642, 13.1%, All LTN), followed by cardiac arrhythmias SMQ (N=100, 2.1%, All LTN), Ischaemic CNS vascular conditions SMQ (N=32, 0.7%, incl. N=12 TIA, N=5 Ischaemic stroke), Embolic and thrombotic events SMQ (N=89, 1.8%, incl. N=14 myocardial infarction, N=15 Deep vein thrombosis, N=12 Pulmonary embolism), Other Ischaemic heart disease SMQ (N=34, 0.7%, incl. N=17 Angina pectoris, N=9 Coronary artery disease).

Common TEAEs

Common TEAE (defined as occurring in $\geq$2% of patients in any LTN-treated dose group and recorded within 48 hours post-dose) increased with dose. By the nature of TEAEs, these were mostly unspecific, however, are reflective of LTN's CNS depressant properties. The most often encountered TEAEs in lasmiditan-treated vs placebo-treated patients of the Phase 2/3 Pool were dizziness (19.9% vs 3.2%), somnolence (7.2% vs 2.3%), paraesthesia (6.4% vs 1.4%), fatigue (5.3% vs 1.0%), nausea (4.9% vs 2.1%), vertigo (2.6% vs 0.2%), asthenia (2.5% vs 0.2%), hypoaesthesia (2.3% vs 0.3%) and muscular

weakness (2.3% vs 0.1%). Some of these may well occur as associated symptom of a migraine attack. For all common TEAEs, the median time to onset was below 1 hour in LTN-treated patients, thereby pointing to a relatedness with LTN intake. On the contrary, the median time to onset in placebo patients for common TEAEs vertigo resp. asthenia was 11.5 resp. 17.7 hours post-dose. In general, common TEAEs were transient, the median duration of common TEAEs in LTN groups ranged from 1.1 hours (paraesthesia) to 4.8 hours (fatigue). The dose related increase in median duration of some of the common TEAEs (somnolence, vertigo, muscular weakness) further points to a causal relationship.

The list of common TEAEs in the All-Lasmiditan Pool was qualitatively identical with the one for the Phase 2/3 Pool and very similar with regard to frequencies of TEAEs, their median onset and duration. All common TEAEs are adequately reflected in section 4.8 of the proposed SmPC.

The vast majority of TEAEs was of mild or moderate intensity. Only a small minority of patients in the Phase 2/3 Pool reported $\geq$ severe TEAEs (3.5%). Dizziness was categorized as severe most often (in N=59 resp. 1.2% of patients). Severe TEAEs were numerically increasing by dose for most TEAEs (dizziness, paraesthesia, fatigue, nausea, vertigo), however, not for all TEAEs (muscular weakness).

A total of 11 treatment emergent SAE were observed in the Phase 2/3 Pool (N=2061 Placebo, N=4861 All LTN). Notably, no TESAE occurred in more than one subject. Hence, the overall number of TESAE is not considered high and there was no signal for accumulation for any of these.

The large number of different PTs were grouped into clusters like Asthenic conditions (HLT) or Disturbances in Consciousness (HLT). For CNS penetrant lasmiditan the overall safety profile points to general CNS depressant features that reveal through dizziness, asthenic conditions (fatigue, lethargy, muscular weakness), paraesthesias, disturbances in consciousness (somnolence, sedation), vertigo, balance disorder, feeling abnormal, or disturbance in attention. However, also the incidence of psychomotor hyperactivity (restlessness), agitation and anxiety significantly separate from placebo. The patient numbers reporting hypotension, hypertension, or bradycardia are low (0.1% in ALL LTN, Phase 2/3 Pool) and do not separate from placebo.

Safety of the second dose

Only patients included in studies 301/302 were given the option of taking a second dose of study medication. Subjects randomised to one of the LTN dose groups for the first dose, were randomized 2:1 to receive either the same LTN dose for the second dose or placebo. The usage of a second dose showed dose response relation. More placebo patients made use of the second dose (762/1262, 60.4%) as compared to those allocated to LTN for the first dose (All LTN, 1307/3177, 41.1%). The portions of subjects requesting a second dose numerically decrease with increasing LTN first dose strength (50, 100, 200 mg). Patient numbers with second doses per dose group are considered large enough to enable an analysis of the second dose safety. The second dose could either be taken for recurrence of pain (i.e. patient responded at 2 hours post-dose) or rescue (patient was not pain free at 2 hours).

The median time from first dose to second dose ranged from 9.5 to 19.3 hours for the lasmiditan dose groups (recurrence). However, the majority of patients requiring a second dose did so for rescue. Irrespective of the time from first to second LTN dose (and associated taking over of first dose PK and AEs into second dose assessment), the Applicant followed a conservative and acceptable approach. For first dose assessment, TEAEs refer to TEAEs occurring within 48 hours after first dose. For second dose assessment, TEAEs refer to TEAEs occurring within 48 hours after the second dose (thereby, any overlap from the first dose is taken over, in case the second dose was taken shortly after the first dose).

The frequency of common TEAEs in the period after the first and before the second dose in studies 301/302 was higher as compared to the frequency of TEAEs in the observation period of 48 hours after the second dose. One may therefore conclude that TEAEs appear to be mainly triggered by the first LTN dose and resolve with time. A second dose of LTN taken within 2-24 hours after the first dose did not

further increase the frequency of TEAEs as compared to patients taking only one LTN dose. No associated SAEs or discontinuations in temporal association to the second dose were reported.

Long-term safety

The frequency of treatment-emergent AEs increases with treatment duration. In the All-Lasmiditan Pool, 55.1% of patients had at least 1 TEAE, compared with 45.7% in lasmiditan-treated patients in the Phase 2/3 Pool. However, the rank order of most frequently recorded TEAEs remains unchanged.

In long-term safety study 305, across all PTs and both LTN dose levels (100 and 200 mg), common TEAEs occurred most often at the first attack within the patient's history of successive migraine attacks. Thereafter, the incidence of TEAEs decreases with increasing numbers of attacks that have been treated. The decrease was already observable with each additional attack across the first 5 attacks, and in the longer run until the 20th attack that has been treated. Hence, tolerability increased with time resp. numbers of attacks in those patients maintaining intermittent treatment with lasmiditan.

There are no controlled data for long-term use of the 5o mg LTN dose, which is less critical from a safety perspective than from the efficacy perspective. Patients entering study 305 were newly randomized to either 100 mg or 200 mg LTN, irrespective of the dose they received in preceding studies 301/302. In principle, patients were initially given the option of a second LTN dose in study 305. However, the option of a second dose was later on restricted with Amendment 2.1 (no second 200 mg dose, second dose not to be taken for rescue). When Amendment 2.1 was implemented, study 305 was already ongoing. Decreasing incident (first occurrence) TEAEs were observed with increasing numbers of attacks treated, irrespective whether patients never, always or sometimes made use of the second LTN dose.

The rates of participants presenting with at least 1 TEAE were considerably higher in multiple attack study LAIJ as compared to studies 301/302. The frequency of TEAEs was highest after the first attack. Thereafter, TEAEs decreased in placebo-controlled study LAIJ across the maximum 4 attacks in a similar way as already observed in long term study 305.

Vital signs

In general, vital signs and quantitative ECG parameters remained stable throughout the placebo-controlled Phase 2/3 Pool in both lasmiditan and placebo treatment groups. However, vital signs resp. ECG parameters were not necessarily assessed in temporal proximity to dosing of lasmiditan (301 / 302: screening + EoS). Therefore, interpretation of any changes observed and their clinical relevance is limited. Instead, in clinical pharmacology studies (LAHU, LAHD, LAIG), where measurement of vital signs was done at regular intervals after dosing, the findings were more pertinent. Mean changes in vital signs (SBP, DBP, pulse) were calculated based on the results of 16 clinical pharmacology studies (data generated either by repetitive BP measuring or ABPM).

Based on ABPM measuring in study LAHU, there was a transient increase in SBP (2.65 mmHg) and DBP (0.95 mmHg) as compared to placebo for about one hour post-dose in non-elderly subjects after SD of LTN 200 mg. The short and transient increase in BP coincides with initial rising of LTN blood levels post-dose. Already 2 hours post-dose, however, BP is lower in subjects that received LTN as compared to placebo and remains lower for about 10 hours.

Similar to the changes in BP observed in non-elderly (study LAHU), initial increases in SBP were observed based on ABPM in elderly subjects in study LAIG. The increase in SBP lasts for about 1-2 hours post-dose and coincides with the rise in blood levels. The increase in SBP was more pronounced in elderly as compared to non-elderly healthy volunteers, however, was not related to dose (SBP change from baseline vs placebo: L100: 5.38 mmHg, L200: 3.75 mmHg). From 3 hours post-dose onwards SBP values in elderly subjects receiving LTN were lower than in elderly receiving placebo.

Changes in vital signs relate to the period of 1-2 hours post-dose for increases in SBP (2.65 mmHg [LTN 200 mg vs placebo] in study LAHU) and up to about 4 hours post-administration for decreases in pulse rate. The decrease in pulse rate following treatment with lasmiditan was consistent across the clinical pharmacology programme (maximum mean decrease from baseline between approximately -5 and -10 bpm following doses of 50 to 200 mg lasmiditan). The frequency of bradycardia (defined as heart rate <50 bpm with decrease ≥15 bpm from baseline, or a "low" change) across all populations was 7.1%, 2.9%, and 4.1% following single dosing with lasmiditan 50 mg, 100 mg, and 200 mg, respectively. This decrease in pulse rate may have implications for the co-administration of lasmiditan with other drugs known to have a similar effect. An additive decreasing effect on HR was shown in PD Interaction study LAHD with propranolol, which is commonly used in migraine prevention. The observed decrease in HR was adequately addressed in SmPC section 4.8.

Abuse liability

Analysis of key abuse liability TEAEs in the Phase2/3 Pool confirmed some abuse liability properties observed in abuse potential study LAHB in recreational drug users. In study LAHB, therapeutic lasmiditan 100 mg and 200 mg doses separated from placebo in terms of increased drug liking, but showed less drug liking and fewer sedative and euphoric effects than the positive control alprazolam 2 mg. There were numerical increases in key AL TEAEs with increasing LTN dose, in particular for Feeling abnormal (PBO: n=1, L50 mg: n=3, L100 mg: n=25, L200 mg: n=26) and to a lesser extent for Euphoric mood, abnormal dreams, and Feeling drunk. The majority of key AL TEAEs were more frequent in lasmiditan-treated patients than in placebo-treated patients. Based on the All-Lasmiditan Pool, key AL TEAEs occurred early (median onset: feeling abnormal 0.8 hours, euphoric mood 0.55 hours) and lasted for 2-3 hours. Most of the reported cases were mild to moderate. LTN's potential abuse liability did not translate into incidences of discrepancies related to missing medication (drug accountability), drug diversion, pertinent overdose, or withdrawal after repetitive dosing.

Cardiovascular Safety – Topic of Interest

There were 58 lasmiditan-treated patients with palpitations (including patients with PTs of palpitations [41], tachycardia [9], and heart rate increased [8]). In the majority of cases (n=41) palpitations occurred concurrently with CNS TEAEs of either dizziness, somnolence, vertigo, paraesthesia, hypoaesthesia and/or tremor. The event of palpitations (including tachycardia and heart rate increased) for most cases was mild to moderate in severity. There were no SAEs of palpitations reported. The exact pulse or change in magnitude of heart rate at the time of the reported event was not known in any patient.

Further rare cases of likely CV TEAEs in LTN patients concern bradycardia / decreased HR (n=3), hypertension / increased BP (n=5), rhythm and other ECG cases (n=3), syncope (n=2), dyspnoea (n=2), or cardiac murmur (n=2). Although figures are low, the relation between bradycardia / decreased HR and lasmiditan is plausible.

The summary of SAEs likely CV in nature in the All-Lasmiditan Pool showed a total of 13 patients with 16 SAEs; 11 patients in addition to those observed in the Phase 2/3 Pool. With regard to the long time that elapsed between last LTN dose, and the background medical history of affected subjects any relation between reported serious cardiovascular AEs in the All-Lasmiditan Pool (covering a 12-month treatment period) and lasmiditan treatment is unlikely.

The incidence of AEs likely CV in nature was checked in patients with categorical changes in vital signs. Based on available data, a relation between categorical changes in vital signs and cardiovascular EAs cannot be established in the All-Lasmiditan Pool.

Whether or not a safety issue can be anticipated in this specific patient subpopulation is considered relevant information, particularly with respect to comparison against the triptans which are known to cause cardiovascular effects and thus are contraindicated in cardiovascular compromised individuals.

Hepatic safety

The overall numbers of patients in the All-Lasmiditan Pool presenting with liver enzyme elevations (ALT, AST, ALP, TBL) were small, and not considered clinically meaningful. However, there was one case fulfilling general Hy's law criteria (AST or ALT ≥3xULN plus TBL ≥ 2xULN). The case concerns a patient that received placebo in study 301 and was randomized to L100 mg in study 305. At the time of study 305 entry, liver values were within the normal range. Relevant AST- and TBL elevations were detected 10 days after the patient took the most recent LTN dose. At this time, the patient had treated 3 migraine attacks using 6 L100 mg doses within the preceding month. About 2 months after detection of hepatic enzyme elevations the patients decided to discontinue. On this day, the patient's ALT, AST and bilirubin were still elevated. The investigator did not consider the hepatic laboratory abnormality as an AE. Hence, the relatedness to the study drug was not collected. Further elucidation by hepatic experts revealed that, given the elevated TBIL of 1.5 mg/dL result prior to initiation of lasmiditan, the referenced subject does not fully fulfil the criteria for categorization as DILI. The meaning of critically elevated hepatic enzymes (in rare cases) to lasmiditan's overall safety was evaluated. The available hepatic-related safety database does not warrant any labelling.

There were 3 additional cases of study discontinuation related to hepatic safety. In each case, patients' liver enzymes were elevated or within normal range at screening of single attack studies 301/302 and exceeded 3-fold ULN after receiving LTN doses. However, all of these were transferred to long term study 305. Two subjects received further LTN doses in study 305 and were finally discontinued due to ongoing liver enzyme elevations. The third patient did not receive LTN during study 305, but was discontinued due AE of liver function test increased.

Suicidal Ideation or Behaviour - Safety Topic of Interest

Suicidal ideation or behaviour was reviewed based on responses to the Columbia Suicide Severity Rating Scale (C-SSRS) and presence of AEs or TEAEs in the SMQ of Suicide/Self-injury. In single attack studies 301/302, C-SSRS assessment was conducted twice (at screening and EoS), in 1-year study 305 C-SSRS were additionally recorded throughout treatment at Visits 1, and 2-5 (covering months 1,3,6,9). Notably, patients responding positive to any question of the C-SSRS were not per se excluded from study participation. Subjects were excluded only if they were at imminent risk of suicide (positive response to Questions 4 or 5 on the C-SSRS). In this context, it is noted that of the 72 patients who reported suicidal ideation or behaviour at baseline, 70 (97.2%) had an improvement in suicidal ideation during study participation. In total, data from patients in the migraine clinical programme do not suggest an increased risk of suicidal ideation or behaviour among those treated with lasmiditan.

2.5.10. Conclusions on the clinical safety

The clinical safety profile of lasmiditan in the acute treatment of migraine attacks was thoroughly and comprehensively characterised in the dossier. By the entirety of available data, the safety profile of CNS active, selective 5-HT1F receptor agonist lasmiditan is considered rather favourable. Lasmiditan was generally well tolerated in large phase 3 RCTs. Some degree of CNS depressant effects was shown, which translate into typical most common TEAEs (dizziness, somnolence, fatigue), propensity to drug abuse and driving impairment. Changes in vital signs were observed in clinical pharmacology trials. They relate to the period of 1-2 hours post-dose for increases in SBP (2.65 mm Hg) and up to 4 hours post-administration for decreases in pulse rate (approx. -5 and -10 bpm following doses of 50 to 200 mg lasmiditan).

2.6. Risk Management Plan

2.6.1. 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

2.6.2. Pharmacovigilance plan

Summary table of Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Anticipated Due Dates
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
			Final Report	31 December 2027
Lasmiditan exposure during pregnancy and adverse pregnancy outcomes (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 (H8HMC-B005: Real-world observational study to assess drug utilisation patterns in the US among migraine patients treated with lasmiditan) (Planned)	- To assess drug utilization 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 - To describe characteristics of lasmiditan-treated patients, including patients treated for longer than 1 year	Drug misuse/abuse (important potential risk) Long-term intermittent use (missing information)	Start of Data Collection	Estimated for 31 December 2021
			Final report	31 December 2023
Long-Term Safety Study (H8HMC-B010: Real-world observational study to assess safety outcomes in the US among migraine patients treated with	– To assess safety outcomes among patients treated with lasmiditan for longer than 1 year - 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

lasmiditan long-term) (Planned)				

2.6.3. Risk minimisation measures

Summary Table of PV 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: 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: H8H-MC-B002 - Observational cohort study of exposure to lasmiditan during pregnancy
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: H8H-MC-B005 -Real-world observational study to assess drug utilisation patterns in the US among migraine patients treated with lasmiditan

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: H8H-MCB010 – Real world observational study to assess the safety outcomes in the US among migraine patients treated with lasmiditan long-term

This summary table of PV and risk minimisation activities by safety concern requires updating, to include study H8H-MC-B005 as additional PV activity to further characterise the missing information of long-term intermittent use (in line with other parts of RMP version 1.0). This study is supposed to identify and describe patients treated beyond 1-year. Study H8H-MC-B005 will also inform on the feasibility of conducting study H8H-MC-B010, which will include patients from study H8H-MC-B005 qualifying for long-term use. As this was considered to be a minor revision, it is agreed it can be implemented in the post-marketing setting (i.e. at the first regulatory opportunity including a proposal for RMP updating).

2.6.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 11 October 2019. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.>

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on*

the readability of the label and package leaflet of medicinal products for human use.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, RAYVOW (lasmiditan) is included in the additional monitoring list as it includes new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Migraine is a serious, chronic, disabling neurological disease characterised by attacks of moderate to severe headache (HA) pain associated with other symptoms such as nausea, vomiting, photophobia, and phonophobia. Migraine attacks typically last from 4 to 72 hours if untreated or unsuccessfully treated. People with migraine may experience an aura prior to the onset of their headache.

3.1.2. Available therapies and unmet medical need

According to current treatment guidelines, unspecific analgesics like acetylic acid, ibuprofen, paracetamol etc. rank among first-line therapies, however, are typically used for less severe migraine attacks. Major progress in more specific treatment of acute migraine symptoms was achieved with the advent of the triptans in the nineties. Triptans target 5-HT1B and 5-HT1D receptors and their mechanism is thought to involve cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release. As the gold standard for acute treatment of migraine, they represent 28% to 36% of prescribed acute migraine medications (Mafi et al. 2015; Molina et al. 2018). However, triptans are not efficacious for all patients: the main efficacy benchmark, i.e. the rates of pain freedom at 2 hours post-dose with triptans are in the range of 20% to 40% (Ferrari et al. 2002). Furthermore, efficacy and tolerability vary, both between agents (7 triptans approved so far), and from patient to patient.

Although forming the mainstay of current acute migraine therapy, it is concluded that around 30% of patients fail to respond to a particular triptan (Dodick DW 2005). The reasons therefore are not fully understood and may include inter- and intra-individual attack variability, on top of other factors modifying responsiveness, like e.g. concomitant use of preventive medication, medication overuse headache (MoH), inadequate dosing, the time point of medication intake relative to the onset of the attack, incomplete absorption due to concomitant gastric stasis or vomiting, presence resp. absence of aura symptoms etc. (Viana M 2013). Furthermore, the use of the triptans is limited with regard to their cardiovascular (CV) risk profile. As evidenced for the leading substance (sumatriptan), triptans are contraindicated in patients with a previous cerebrovascular accident (CVA), transient ischemic attack (TIA), moderately severe or severe hypertension, or untreated mild hypertension, peripheral vascular disease, established CAD, including ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or Prinzmetal’s angina.

Overall, in view of incomplete response to currently available acute migraine medications on the one side and limitations to their use due to CV safety concerns on the other side, there is a general need for new therapeutic approaches in acute migraine therapy. Based on its pharmacological profile as a selective 5-HT1F receptor agonist and the claimed absence of any vasoconstrictive properties, LTN may potentially constitute a valuable contribution to the currently available therapeutic armamentarium.

3.1.3. Main clinical studies

A comprehensive data package was provided to show efficacy of lasmiditan (LTN) as an acute treatment for migraine attacks. It includes three pivotal double-blind, placebo-controlled studies. LTN may be seen as a first-in-class substance, another selective 5-HT1F receptor agonist has not been approved yet. To provide a sound database that enables to check for reproducibility, two independent single attack trials (essentially similar in design) were conducted in the US and Europe (studies 301 [N=2.231, US] and 302 [N=3.005, US, UK, Germany]).

Consistency of effect across multiple attacks was analysed in study LAIJ (N=1613). The long-term intermittent use of LTN was examined within the scope of open-label safety study 305, which provides supportive efficacy data in all treated attacks over one year (N=1.954 mITT patients, n=17.329 mITT attacks treated).

Essential aspects of the phase III program like the International Headache Society (HIS) diagnostic criteria (code 1.1 *Migraine without aura* or 1.2.1 *Migraine with typical aura*), choice of target population, endpoints and mix of proven efficacy in single attacks resp. consistency of effect over four attacks are concordant with current EMA and IHS guideline provisions. Largely analogous studies were conducted in support of MAAs for the triptans.

Efficacy endpoints across all 3 studies included assessment of freedom from pain at 2 hours post-dose (primary), freedom from the most bothersome symptom (MBS, chosen from photophobia, phonophobia, or nausea) at 2 hours post-dose (key secondary in 301/302), pain relief, sustained pain freedom over 24 resp. 48 hours, onset of action, migraine-related disability, associated migraine symptoms, PGIC, need for additional interventions, and incidence of migraine recurrence. Apart from pain freedom at 2 hours for the first attack, the portion of patients pain free at 2 hours in at least 2 out of 3 attacks was specified as co-primary in consistency trial LAIJ. Overall, the entirety of primary, key secondary and secondary endpoints was defined along guideline recommendations.

In single attack study 301 subjects were randomized 1:1:1 to treat the acute migraine attack with LTN 100 mg, LTN 200 mg or placebo. In the parallel single attack study 302 an additional 50 mg LTN dose arm was included. No controlled data were generated to support consistency of effect across 4 attacks for the 50 mg LTN dose.

Throughout single attack studies patients had the option to take a second dose up to 24 hours after the first dose in case the patient was pain-free after 2 hours but pain recurred (second dose as recurrence) or if the patient did not respond 2 hours after the first dose (second dose as rescue). The second dose was randomized 2:1 to correspond to the same strength as the first dose or placebo.

The importance of placebo response encountered in migraine trials is well established. Inclusion of placebo control in the clinical trial program of LTN is endorsed. On the other side, including an active comparator arm (e.g. triptan) would have been useful to contextualize the clinical effect achieved with LTN, however, is considered not essential and difficult to accomplish in the present case given the differences between LTN and triptans in terms of treating migraine patients with CV comorbidity.

The two single attack studies 301 and 302 were identical in terms of exclusion criteria with the exception of the following three cardiovascular conditions: known coronary artery disease (CAD), clinically

significant arrhythmia, or uncontrolled hypertension. While these were excluded in study 301, migraine patients presenting with these CV comorbidities were eligible for participating in study 302 or LAIJ. Study 301 (Apr 2015 – Aug 2016) and study 302 (May 2016 – Jun 2017) were not conducted simultaneously. Gaining insight in LTN's safety profile obtained from study 301 may have influenced the sponsor's decision to define less stringent exclusion criteria in study 302. Patients with less critical CV risks like controlled hypertension, high cholesterol, uncomplicated diabetes etc. were not excluded in either of the studies. It is therefore noted that LTN trials included a subgroup of subjects with CV comorbidity for which the use of triptans would formally be contraindicated. There is no statement in the proposed lasmiditan SmPC actively highlighting or claiming a potential advantage of LTN as compared to triptans in terms of the CV risk profile.

As concerns baseline demographics, the primary analysis population is considered typically representative of the migraine target population in terms of age (mean of 42 years, 96.5% < 65 years), gender (84.4% female), history of migraine with aura (38.4%), and duration of disease history (mean of 18.3 years).

Recruited subjects are rather severely affected by the disease as reflected by the average number of migraines per month in past 3 months at baseline (5.15 [1.84]) and the mean migraine disability MIDAS Total Score of 31.8 (21.7). Accordingly, about one quarter of subjects was on stable migraine prevention medication (23.7% in the pooled population, highest portion in consistency trial LAIJ: 30.3%). In phase III trials, subjects with a history of chronic migraine (CM) were excluded. The average total number of days with headache in past 3 months (17.7 [10.2]) reported by participants is in line with the episodic migraine (EM) diagnosis.

Long-term data for the intermittent, acute treatment of migraine attacks with lasmiditan for up to 1 year were obtained from open label study 305. Mainly subjects taken over from previous studies 301/302 were recruited, apart from a minority of lasmiditan-naïve subjects for which the study was opened upon implementation of Protocol Addendum 2. Irrespective of the dose received in preceding studies 301/302, subjects were newly randomized (1:1) to LTN 100 mg or 200 mg. The lasmiditan 50 mg dose was not tested long term in study 305.

3.2. Favourable effects

The clinical benefit of lasmiditan for the treatment of acute migraine attacks was shown by significant superiority over placebo along primary and key secondary endpoints.

The majority of treated migraine attacks within the Primary Analysis Population was of moderate (69.5 – 72.0%) or severe (23.1 – 28.9%) intensity. The subjects administered the study medication fairly early, with a median time of 60-70 minutes after the onset of a migraine attack. In more than 90% of all attacks in the Primary Analysis Population subjects could identify one of the associated symptoms as most bothersome. Photophobia was recorded most often as MBS (47.7%), followed by nausea (24.5%) and phonophobia (20.4%).

Efficacy in single attacks

The common primary endpoint across the two single attack studies 301/302 and consistency trial LAIJ (focused on the first of up to four migraine attacks) showed statistically significant superiority over placebo across all LTN doses (50, 100, 200 mg). With increasing LTN doses numerically higher portions of subjects were pain free at 2 hours (301: L200 mg: 32.2%, L100 mg: 28.2%, PBO: 15.3%; 302: L200 mg: 38.8%, L100 mg: 31.4%, 50 mg: 28.6%, PBO: 21.3%; LAIJ: L200 mg: 29.3%, L100 mg: 25.8%, PBO: 8.4%). The overall magnitude of effect is in a similar range or somewhat lower as what could be shown for most triptans in previous studies. Across all RCTs including sumatriptan a net (placebo-

subtracted) effect of 19% [95% CI 17-22] was calculated for sumatriptan 100 mg. For rizatriptan 10 mg and eletriptan 80 mg net effects over placebo are even considerably higher (around 30%, Ferrari MD 2002).

Along the same lines, for the key secondary endpoint, statistically more patients achieved MBS freedom at the 2-hour assessment time point across all LTN dose arms (50, 100, 200 mg) as compared to placebo. In absolute figures, the portions of patients achieving pain relief across doses and double-blind studies are higher (54-65%) as compared to portions observed for pain freedom (26-39%), which could be expected given that pain relief is considered easier to achieve than pain freedom. If compared to placebo, statistical superiority could be demonstrated for each LTN dose arm (50,100,200 mg) across studies 301/302/LAIJ.

The onset of pain relief is a crucial aspect of efficacy. The portions of patients achieving pain freedom were assessed based on their e-diary entries at 0.5-hours intervals post-dose. One hour after IMP intake the 100 and 200 mg LTN dose arm statistically significant separated from placebo. As time post-dose progressed, the portions of patients reporting to be pain-free increased per dose arm until the 2-hour post-dose primary assessment time point. For the lowest 50 mg LTN dose arm, statistically more patients reached pain freedom from 1.5 hours post-dose onwards. The benefit of early intervention in the course of a migraine attack was previously established in triptan therapy.

Recurrence of pain

In migraine therapy, recurrence of pain is observed in a subgroup of patients, i.e. these subjects respond at the 2-hours primary assessment time point (i.e. are pain free 2 hours post-dose), however, pain recurs within the subsequent course of 24 resp. 48 hours post-dose. To address efficacy in this subgroup of patients the secondary endpoint of sustained pain freedom 24 resp. 48 hours post-dose was examined. As delineated above, it can roughly be observed that about one third of subjects was pain free at 2 hours (primary endpoint, mITT). About half of those 2-hour pain free responders actually reports sustained pain freedom over 24 (24 hours sustained pain free: 301: 14.8% [100 mg], 18.6% [200 mg]; 302: 17.9% [100 mg], 22.7% [200 mg], ITT) resp. 48 hours (48 hours sustained pain free: 301: 14.9% [100 mg], 16.4% [200 mg]; 302: 15.1% [100 mg], 19.6% [200 mg], ITT). Hence, the vast majority of migraine patients sustained pain free at 24 hours, is also pain free at 48 hours. Across LTN dose arms and pivotal trials (301, 302, LAIJ) lasmiditan demonstrated placebo superiority apart from the 50 mg dose examined in study 302 (50 mg vs placebo: at 24 hours p=0.072, at 48 hours p=0.129) and the 100 mg dose arm in study 302 for 48 hours (p=0.117). However, the LTN 100 mg significantly separated from placebo at 24 hours (p=0.041). Interpretation of results for the sustained pain free endpoint should take into account that in PK studies lasmiditan was eliminated with a mean t1/2 value of about 5.7 hours. Furthermore, the sustained pain free secondary endpoint was assessed only in those patients having not used any additional migraine intervention following the first dose.

Consistency of effect

In terms of consistency of effect, highly significant superiority over placebo could be shown for both LTN doses (100, 200 mg) in terms of the primary consistency endpoint in study LAIJ, pain freedom at 2 hours in 2 out of 3 attacks (placebo: 4.3%, L100 mg: 14.4%, L200 mg: 24.4%, ITT consistency population). Significant results were also obtained for pain relief and consistency across 2 out of 3 attacks in the subgroup of triptan insufficient responders (TIR).

Supportive efficacy data are derived from open label long term study 305, which primarily recruited subjects taken over from studies 301/302. The overall portion of attacks that is successfully treated (i.e. achieved pain freedom at 2 hours post-dose) observed throughout 1-year treatment period (L100 mg: 26.7%, L200 mg: 32.2%) closely reproduces the portions achieved in the controlled single attack studies (301: L100 mg: 28.2%, L200 mg: 32.2%; 302: L100 mg: 31.4%, L200 mg: 38.8%). As can be expected

given the overall discontinuation rate of 52.2%, the number of attacks treated per quarter decreases in the course of the trial, the portion of successfully treated attacks, however, does not (L100 mg: Q1: 27.3%, Q4: 29.6%; L200 mg: Q1: 32.7%, Q4: 31.2%).

Apart from analyses of attacks treated per quarter, it was also examined how treatment success evolves in patients with a large number of attacks suffered throughout the open label treatment course. Attacks were numbered as 1,2,3.. up to 20 relative to their order in a patient's history of treated attacks in study 305. For the treatment of up 20 attacks, the portion of successfully treated attacks (in terms of 2 hours pain freedom) only slightly decreases from attack 1 (36.6%) to attack 20 (31.5%) in the 200 mg LTN dose arm, while for the 100 mg LTN efficacy decreased more evidently from attack 1 (33.2%) to attack 20 (22.5%). The portions of treatment success in terms of 2 hours MBS freedom evolved in a similar way. However, the data should be interpreted with caution given the differences in the underlying database of treated attacks: attack 1 (L100 mg: N=969, L200 mg: N=983), attack 20 (L100 mg: N=120, L200 mg: L=111). Overall, supportive efficacy data obtained from long-term study 305 demonstrate maintenance of clinical benefit if lasmiditan is used intermittently for acute migraine attacks over 1 year.

3.3. Uncertainties and limitations about favourable effects

Beyond consistent superiority of lasmiditan across primary and key secondary endpoints and LTN doses, there are a number of uncertainties resp. limitations in the efficacy-related clinical data package that pertain to the following points.

Limited data package to support the 50 mg dose

There are no controlled data or supportive data to demonstrate the efficacy of the 50 mg lasmiditan dose across multiple migraine attacks. Long-term study 305 did not include the 50 mg dose arm. The lasmiditan 50 mg dose was tested in study 302 and in consistency trial LAIJ in the placebo arms, when LTN 50 mg was applied to treat the third or fourth attack. In both clinical settings the net effect over placebo in terms of 2-hours pain freedom was modest, however, statistically significant (302: net effect 7.3 , Odds ratio 1.5 [1.1, 1.9], p=.003; LAIJ: net effect 7.1 , Odds ratio 1.8 [1.1, 3.0], p=.015). Available efficacy data for the 50 mg dose align with the almost consistent dose-response that was observed across endpoints, i.e. are modest as compared to the 100 and 200 mg lasmiditan dose in terms of pain and MBS freedom. The modest effect also translates into about 30 min later onset of effect or failure to achieve significant sustained pain freedom over 24 resp. 48 hours post-dose over placebo.

It is therefore concluded that the B/R balance for the 50 mg strength is positive despite incompleteness of the underlying database. In the revised posology section of the SmPC it is specified that 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.

Efficacy of lasmiditan across various associated symptoms

The presence of photophobia, phonophobia, nausea, and vomiting at 2 hours was assessed for studies 301, 302, and LAIJ, regardless of whether the patient reported the symptom at baseline resp. categorized the associated symptom as most bothersome. While all doses of LTN (50, 100, 200 mg) statistically significantly reduced the portions of subjects with presence of photophobia or phonophobia as compared to placebo at 2 hours post-dose, other associated symptoms like nausea or vomiting were virtually unaffected by lasmiditan. The portions of subjects reporting vomiting are very low (1-2% across studies), however, a meaningful portion of subjects was nauseous at 2 hours post-dose (about 18-23% across studies 301/302). One may hypothesize that the differential effect of LTN on the different migraine associated symptoms (phonophobia / photophobia on the one side, nausea / vomiting on the other side)

could be explained by different pathophysiological mechanisms causing the associated symptoms, with the one being affected by 5-HT1F agonism while the others aren't. Nausea was identified as most bothersome in 24.5% of attacks in the pooled population (301: 22.5%, 303: 21.9%, LAIJ: 31.9%).

LTN not effective as second dose taken for rescue

If taken for recurrence, clear numerical benefit in terms of pain resp. MBS freedom at 2 hours could be shown for the second LTN dose. However, efficacy data for LTN second doses taken for rescue are less favourable. At the 2 hour post-dose assessment time point, the effect of the second LTN dose, taken for rescue, i.e. in those subjects not achieving pain freedom 2 hours after the first dose, numerically does not separate from placebo (LTN/PBO) across the pooled LTN dose groups (LTN/LTN). If the patient did not respond to the first dose of LTN, the second LTN dose taken for rescue is not considered to provide meaningful benefit in terms of pain resp. MBS freedom. Accordingly, SmPC section 4.2 proposed for LTN correctly specifies that *if the migraine attack has not resolved after taking a single LTN dose, a second dose has not been shown to be effective for the same attack.*

LTN as a second dose for recurrence

Second dosing for recurrence was defined for patients who were pain free at 2 hours and then took a second dose of study drug between 2 and 24 hours after first dose. The number of people who took a second dose of study medication for recurrence in the 2 trials (Studies 301 and 302) and had second dose efficacy data was limited (n = 93 total; n = 73 with lasmiditan as the first dose). The results show a numerical advantage for a second dose of lasmiditan for the treatment of recurrence.

To contextualize the number of n=73 affected subjects, it is considered helpful to illustrate the flow of patients. The ITT population of subjects receiving LTN as first dose within the single attack studies 301/302 is composed of N=2851 subjects. Of these, n=902 subjects were pain free at 2 hours and are therefore potentially eligible for the ITT-Second Dose Recurrence Population. However, only a small portion of n=73 actually took a second dose of study drug for recurrence, i.e. 73/2851 [2.6%] of the ITT population receiving LTN in studies 301/302. Relative to those n=902 subjects being pain free at 2 hours, the portion of subjects choosing a second dose for recurrence is 73/902 [8.1%]. In view of the small number of affected patients it is evident that demonstration of statistically significant effects can hardly be achieved. Nonetheless, there were numerical advantages in favour of the second LTN dose observed in the pooled LTN/LTN group as compared to LTN/PBO across the main efficacy endpoints at the 2-hour post-dose time point (pain free: LTN/PBO 32.0%, LTN/LTN 50.0%; MBS free: LTN/PBO 40.9%, LTN/LTN 70.7%).

In essence, the favourable effect of the second dose of LTN taken for recurrence as compared to placebo is observed across all LTN doses (50, 100, 200 mg) and most meaningful endpoints (pain resp. MBS freedom 2 hours, pain relief). However, broken down to the single LTN doses, the number of affected subjects is so low that statistical significance could not be shown. No more than 200 mg should be taken in 24 hours. Limitation of the MDD to 200 mg is derived from driving impairment studies where a significant impact on driving ability was found and only doses of up to 200 mg were tested. In consistency trial LAIJ, patients were not given the option of a second dose, thereby limiting the database. Overall, the option for taking a second dose for headache recurrence is supported. In alignment with triptan posology, a posology recommendations for administration of 2nd lasmiditan doses in case of recurrent pain was introduced in SmPC section 4.2, taking due account on dose limitations (MDD of 200 mg) and time (2nd dose not to be taken within 2 hours after the initial dose)

Subgroup of migraineurs not responding to lasmiditan

The phenomenon of non-response to triptans in a subgroup of patients was described in literature reports (Dodick DW 2005). As concerns potential non-response to lasmiditan, the exploratory analysis of headache pain freedom across the maximum treated 4 attacks in consistency trial LAIJ adds further

insight into the consistency of effect observed for LTN. Differentiating between subgroups having experienced either 2, 3 or 4 attacks throughout the double-blind treatment period, the rate of subjects not achieving pain freedom in any of these is around 18-23% across subgroups and LTN doses (100 mg, 200 mg). Hence, there was a group of around 20% of patients that could not successfully treat a single attack in multiple attack trial LAIJ. Optimum treatment success, i.e. pain freedom for each of the 4 attacks, is achieved only by a minority of 1.8% (L100 mg) resp. 2.9% (L200 mg) of subjects. On the other side, a statistically significant higher portion of subjects achieved pain freedom in 3 out of 4 attacks (L100 mg: 7.4%, OR 3.01, p=0.004; L200 mg: 10.8%, OR 4.58, p<.001) as compared to control (2.6%).

Fixed dose assignment in RCT – no option to individual dose adaptation

Throughout all pivotal trials, patients were randomly allocated to fixed LTN dose arms without the option to adapt the dose to the individual patient's need in the course of the study. This way, consistent superiority over placebo was shown across all dose arms (50, 100, 200 mg) in terms of most relevant efficacy measures. Hence, the clinical database does not fully elucidate which LTN dose should actually be chosen in LTN treatment initiation in clinical practice.

Based on available efficacy data, the proposed posology wording was endorsed as indeed higher treatment success rates were observed with increasing doses.

3.4. Unfavourable effects

Safety database

The database for the safety characterization of lasmiditan in terms of overall exposure was broad. The Phase 2/3 Pool, used for the primary safety analyses, includes a total of 6922 patients (lasmiditan, n = 4861; placebo, n = 2061). There were a total of 2030 patients in the long-term open-label safety study (305/LAHL), and as of the data cut-off for this submission, there were 401 patients in Study LAIJ-OLE. The All-Lasmiditan Pool comprised 5916 lasmiditan-treated patients. The minimum requirements for long term exposure over ≥6 (N=365) resp. 12 months (N=186) according to ICH E1 are met. The study population is considered to closely reflect targeted migraine patients encountered in clinical practice. Around 3.5% of the safety population was older than 65 years old. Patients with a history of cardiovascular disease were not excluded. A portion of 16.3% (All LTN) of subjects presented with relevant baseline cardiovascular disease.

Common TEAEs

The AE profile demonstrated that lasmiditan was generally well tolerated. Common TEAE (defined as occurring in ≥2% of patients in any LTN-treated dose group and recorded within 48 hours post-dose) increased with dose. By the nature of TEAEs, these were mostly unspecific, however, are reflective of LTN's CNS depressant properties. The most often encountered TEAEs in lasmiditan-treated vs placebo-treated patients of the Phase 2/3 Pool were dizziness (19.9% vs 3.2%), somnolence (7.2% vs 2.3%), paraesthesia (6.4% vs 1.4%), fatigue (5.3% vs 1.0%), nausea (4.9% vs 2.1%), vertigo (2.6% vs 0.2%), asthenia (2.5% vs 0.2%), hypoaesthesia (2.3% vs 0.3%) and muscular weakness (2.3% vs 0.1%). Some of these may well occur as associated symptom of a migraine attack. For all common TEAEs, the median time to onset was below 1 hour in LTN-treated patients, thereby pointing to a relatedness with LTN intake. In general, common TEAEs were transient, the median duration of common TEAEs in LTN groups ranged from 1.1 hours (paraesthesia) to 4.8 hours (fatigue). The dose related increase in median duration of some of the common TEAEs (somnolence, vertigo, muscular weakness) further points to a causal relationship.

The list of common TEAEs in the All-Lasmiditan Pool was qualitatively identical with the one for the Phase 2/3 Pool and very similar with regard to frequencies of TEAEs, their median onset and duration. All common TEAEs are adequately reflected in section 4.8 of the proposed SmPC.

The vast majority of TEAEs was of mild or moderate intensity. Only a small minority of patients in the Phase 2/3 Pool reported ≥ severe TEAEs (3.5%). Dizziness was categorized as severe most often (in N=59 resp. 1.2% of patients). Severe TEAEs were numerically increasing by dose for most TEAEs (dizziness, paraesthesia, fatigue, nausea, vertigo), however, not for all TEAEs (muscular weakness).

A total of 11 treatment emergent SAE were observed in the Phase 2/3 Pool (N=2061 Placebo, N=4861 All LTN). Notably, no TESAE occurred in more than one subject. Hence, the overall number of TESAE is not considered high and there was no signal for accumulation for any of these.

CNS Depressant effect – Driving impairment – Abuse liability

The large number of different PTs were grouped into clusters like Asthenic conditions (HLT) or Disturbances in Consciousness (HLT). For CNS penetrant lasmiditan the overall safety profile points to general CNS depressant features that reveal through dizziness, asthenic conditions (fatigue, lethargy, muscular weakness), paraesthesias, disturbances in consciousness (somnolence, sedation), vertigo, balance disorder, feeling abnormal, or disturbance in attention. However, also the incidence of psychomotor hyperactivity (restlessness), agitation and anxiety significantly separate from placebo. The patient numbers reporting hypotension, hypertension, or bradycardia are low (0.1% in ALL LTN, Phase 2/3 Pool) and do not separate from placebo.

The CNS depressant profile in terms of common TEAEs aligns with clinical pharmacology data obtained in two driving impairment studies. In both studies the same Standard Deviation Lateral Position (SDLP) primary endpoint was measured, i.e. exceedance from driving lane throughout a 62.1 mile (100 km), approximately 60 minute, monotonous, two-lane highway driving task by simulated driving performance using CRCDS-MiniSim. In the first Study 106 driving performance was tested 90 min post-dose, i.e. during the approximate time of LTN peak concentration. Exceedance from driving lane increased in a dose dependent manner during the simulated driving performance test (exceedance in cm for LTN doses 50, 100, 200 mg over placebo: 9.9, 15.4, 21.1 cm, respectively). Therefore, the a priori safety threshold of 4.4 cm exceedance (corresponding to about 0.05% blood alcohol), was exceeded indicating a significant driving impairment effect for LTN. For the highest 200 mg LTN doses the deviation from lateral position (SDLP) did not differ from the one observed for the 1 mg alprazolam active control. Significant driving impairment around Tmax (2 – 2.5 hours) was shown across the three LTN doses tested in study 106, corresponding to those proposed for marketing. Secondary driving endpoints, cognitive test results, and self-report measures provide further support that lasmiditan had a significant dose-dependent impact on driving.

The subsequent driving performance study LAIF examined how long driving impairment actually lasts after SD dosing of LTN 100 mg and 200 mg (including sedative antihistamine, short acting diphenhydramine 50 mg as active control). Driving ability was tested by three consecutive driving performance tests conducted at 8, 12 and 24 hours post-dose. Already 8 hours post-dose LTN doses of 100 or 200 mg did not impair driving performance to a relevant degree. It can therefore be concluded that the significant driving impairment found around Tmax of LTN (2 – 2.5 hours post-dose) in study 106 does not last for up to 8 hours post-dose. Since doses of up to 200 mg lasmiditan were tested for driving impairment, the MDD was limited to 200 mg, i.e. subjects receiving 200 mg LTN as first dose do not have the option for a second dose within 24 hours. The driving impairment effect found for lasmiditan is adequately addressed by a warning note in SmPC section 4.4. In the context of clinical trials where patients were asked not to drive for 12 hours (Studies 301, 302, and 305) or 8 hours (Studies LAIH and LAIJ), there is no clear evidence of an association between lasmiditan use and motor vehicle accidents.

In terms of abuse liability (AL), analysis of key AL TEAEs in the Phase2/3 Pool confirmed some abuse liability properties observed in abuse potential study LAHB in recreational drug users. In study LAHB, therapeutic lasmiditan 100 mg and 200 mg doses separated from placebo in terms of increased drug liking, but showed less drug liking and fewer sedative and euphoric effects than the positive control alprazolam 2 mg. The majority of key AL TEAEs were more frequent in lasmiditan-treated patients than in placebo-treated patients. Based on the All-Lasmiditan Pool, key AL TEAEs occurred early (median onset: feeling abnormal 0.8 hours, euphoric mood 0.55 hours) and lasted for 2-3 hours. Most of the reported cases were mild to moderate. LTN's potential abuse liability did not translate into incidences of discrepancies related to missing medication (drug accountability), drug diversion, pertinent overdose, or withdrawal after repetitive dosing.

Safety of the second dose

Administration of a second LTN dose, either taken for rescue or recurrence, did not increase the frequency of TEAEs. Only patients included in studies 301/302 were given the option of taking a second dose of study medication. The usage of a second dose showed dose response relation. More placebo patients made use of the second dose (762/1262, 60.4%) as compared to those allocated to LTN for the first dose (All LTN, 1307/3177, 41.1%). The portions of subjects requesting a second dose numerically decrease with increasing LTN first dose strength (50, 100, 200 mg). Patient numbers with second doses per dose group are considered large enough to enable an analysis of the second dose safety. The frequency of common TEAEs in the period after the first and before the second dose in studies 301/302 was higher as compared to the frequency of TEAEs in the observation period of 48 hours after the second dose. One may therefore conclude that TEAEs appear to be mainly triggered by the first LTN dose and resolve with time. A second dose of LTN taken within 2-24 hours after the first dose did not further increase the frequency of TEAEs as compared to patients taking only one LTN dose. No associated SAEs or discontinuations in temporal association to the second dose were reported.

Long-term safety

The frequency of treatment-emergent AEs increases with treatment duration. In the All-Lasmiditan Pool, 55.1% of patients had at least 1 TEAE, compared with 45.7% in lasmiditan-treated patients in the Phase 2/3 Pool. However, the rank order of most frequently recorded TEAEs remains unchanged.

In long-term safety study 305, across all PTs and both LTN dose levels (100 and 200 mg), common TEAEs occurred most often at the first attack within the patient's history of successive migraine attacks. Thereafter, the incidence of TEAEs decreases with increasing numbers of attacks that have been treated. The decrease was already observable with each additional attack across the first 5 attacks, and in the longer run until the 20th attack that has been treated. Hence, tolerability increased with time resp. numbers of attacks in those patients maintaining intermittent treatment with lasmiditan.

Vital signs

In general, vital signs and quantitative ECG parameters remained stable throughout the placebo-controlled Phase 2/3 Pool in both lasmiditan and placebo treatment groups. However, vital signs resp. ECG parameters were not necessarily assessed in temporal proximity to dosing of lasmiditan (301 / 302: screening + EoS). Therefore, interpretation of any changes observed and their clinical relevance is limited. Instead, in clinical pharmacology studies (LAHU, LAHD, LAIG), where measurement of vital signs was done at regular intervals after dosing, the findings were more pertinent. Mean changes in vital signs (SBP, DBP, pulse) were calculated based on the results of 16 clinical pharmacology studies (data generated either by repetitive BP measuring or ABPM).

Based on ABPM measuring in study LAHU, there was a transient increase in SBP (2.65 mmHg) and DBP (0.95 mmHg) as compared to placebo for about one-hour post-dose in non-elderly subjects after SD of LTN 200 mg. The short and transient increase in BP coincides with initial rising of LTN blood levels post-

dose. Already 2 hours post-dose, however, BP is lower in subjects that received LTN as compared to placebo and remains lower for about 10 hours.

Similar to the changes in BP observed in non-elderly (study LAHU), initial increases in SBP were observed based on ABPM in elderly subjects in study LAIG. The increase in SBP lasts for about 1-2 hours post-dose and coincides with the rise in blood levels. The increase in SBP was more pronounced in elderly as compared to non-elderly healthy volunteers, however, was not related to dose (SBP change from baseline vs placebo: L100: 5.38 mmHg, L200: 3.75 mmHg). From 3 hours post-dose onwards SBP values in elderly subjects receiving LTN were lower than in elderly receiving placebo.

Changes in vital signs relate to the period of 1-2 hours post-dose for increases in SBP (2.65 mmHg [LTN 200 mg vs placebo] in study LAHU) and up to about 4 hours post-administration for decreases in pulse rate. The decrease in pulse rate following treatment with lasmiditan was consistent across the clinical pharmacology programme (maximum mean decrease from baseline between approximately -5 and -10 bpm following doses of 50 to 200 mg lasmiditan). The frequency of bradycardia (defined as heart rate <50 bpm with decrease $\geq$15 bpm from baseline, or a "low" change) across all populations was 7.1%, 2.9%, and 4.1% following single dosing with lasmiditan 50 mg, 100 mg, and 200 mg, respectively. This decrease in pulse rate may have implications for the co-administration of lasmiditan with other drugs known to have a similar effect. An additive decreasing effect on HR was shown in PD Interaction study LAHD with propranolol, which is commonly used in migraine prevention. The observed decrease in HR was adequately addressed in SmPC section 4.8.

Cardiovascular Safety – Topic of Interest

There were 58 lasmiditan-treated patients with palpitations (including patients with PTs of palpitations [41], tachycardia [9], and heart rate increased [8]). In the majority of cases (n=41) palpitations occurred concurrently with CNS TEAEs of either dizziness, somnolence, vertigo, paraesthesia, hypoaesthesia and/or tremor. The event of palpitations (including tachycardia and heart rate increased) for most cases was mild to moderate in severity. There were no SAEs of palpitations reported. The exact pulse or change in magnitude of heart rate at the time of the reported event was not known in any patient.

Further rare cases of likely CV TEAEs in LTN patients concern bradycardia / decreased HR (n=3), hypertension / increased BP (n=5), rhythm and other ECG cases (n=3), syncope (n=2), dyspnoea (n=2), or cardiac murmur (n=2). Although figures are low, the relation between bradycardia / decreased HR and lasmiditan is plausible.

The summary of SAEs likely CV in nature in the All-Lasmiditan Pool showed a total of 13 patients with 16 SAEs; 11 patients in addition to those observed in the Phase 2/3 Pool. With regard to the long time that elapsed between last LTN dose, and the background medical history of affected subjects any relation between reported serious cardiovascular AEs in the All-Lasmiditan Pool (covering a 12-month treatment period) and lasmiditan treatment is unlikely.

The incidence of AEs likely CV in nature was checked in patients with categorical changes in vital signs. Based on available data, a relation between categorical changes in vital signs and cardiovascular EAs cannot be established in the All-Lasmiditan Pool.

Rare case of critical liver enzyme elevations

There was one case fulfilling general Hy's law criteria (AST or ALT $\geq$3xULN plus TBL $\geq$ 2xULN). At the time of study 305 entry, liver values were within the normal range. Relevant AST- and TBL elevations were detected 10 days after the patient took the most recent LTN dose. At this time, the patient had treated 3 migraine attacks using 6 L100 mg doses within the preceding month. About 2 months after detection of hepatic enzyme elevations (according to Hy's law) the patients decided to discontinue. On this day, the patient's ALT, AST and bilirubin were still elevated.

3.5. Uncertainties and limitations about unfavourable effects

The risks and unfavourable effects potentially associated with the use of lasmiditan were carefully and comprehensively characterized through clinical pharmacology and RCTs. The key risks of lasmiditan are considered to constitute impaired ability to drive/operate machinery and drug misuse/abuse. These are adequately addressed in the proposed SmPC.

Most uncertainty concerns lasmiditan's potential to induce critical liver enzyme elevations in rare cases.

3.6. Effects Table

Table 56: Effects Table of Lasmiditan for Use in the Acute Treatment of Migraine with or without Aura in Adults

Effect	Short Description	PBO	LTN 50 mg	LTN 100 mg	LTN 200 mg	L50 mg – PBO (%)	L100 mg – PBO (%)	L200 mg – PBO (%)	Strengths / Uncertainties / Limitations
Favourable Effects[a]									
Pain freedom at 2 hours	n (%) Pain freedom: reduction in pain severity from mild, moderate, or severe at baseline to none	301: 80 (15.3)	---	142 (28.2)	167 (32.2)	---	**12.9***	**16.9***	• Study population representative for clinical practice • Primary endpoint (2 hour pain free) met across all doses and studies • Magnitude of effect similar to / somewhat lower than triptans • Key secondary endpoint (2 hours MBS free) met across all doses and studies • Within patient consistency of effect shown in 2/3 attacks • Onset of effect partly significant at time points earlier than 2 hours post-dose • Uncertain efficacy against nausea as associated symptom
		302: 115 (21.3)	159 (28.6)	167 (31.4)	205 (38.8)	**7.3***	**10.1***	**17.5***	
		LAIJ: 37 (8.4)	---	108 (25.8)	127 (29.3)	---	**17.4***	**20.9***	
Consistency of effect	n(%) Pain freedom at 2 hours in at least 2 out of 3 attacks	LAIJ: 16 (4.3)	---	49 (14.4)	82 (24.4)	---	**10.1***	**20.1***	
MBS freedom at 2 hours	n(%) MBS free: absence of associated migraine symptom (nausea, phonophobia, or photophobia)	301: 144 (29.5)	---	192 (40.9)	196 (40.7)	---	**11.4***	**11.2***	
		302: 172 (33.5)	209 (40.8)	221 (44.2)	235 (48.7)	**7.3***	**10.7***	**15.2***	
		LAIJ: 111 (28.0)	---	152 (40.4)	154 (39.0)	---	**12.4***	**11.0***	
Pain relief at 2 hours	n (%) Pain relief: reduction in	301: 217 (39.2)	---	304 (54.1)	303 (54.6)	---	**14.9***	**15.4***	

Effect	Short Description	PBO	LTN 50 mg	LTN 100 mg	LTN 200 mg	L50 mg – PBO (%)	L100 mg – PBO (%)	L200 mg – PBO (%)	Strengths / Uncertainties / Limitations
	pain from moderate or severe to mild or none, or from mild to none	302: 258 (44.9)	332 (55.5)	341 (59.7)	343 (60.7)	**10.6***	**14.8***	**15.8***	• Uncertain choice of dose in treatment initiation • Significant sustained pain freedom achieved with L200 mg over 24 and 48 hours post-dose and for L100 mg over 24 hours post-dose, however, L50 mg only numerically better than placebo
		LAIJ: 183 (41.3)	---	274 (65.4)	283 (65.2)	---	**24.1***	**23.9***	
Sustained Pain Freedom – at 24 hours	n (%) Sustained pain freedom: headache pain free 2 and 24 hours after first dose, without using any medications after first dose.	301: 42 (7.6)	---	83 (14.8)	103 (18.6)	---	**7.2***	**11.0***	
		302: 77 (13.4)	103 (17.2)	102 (17.9)	128 (22.7)	3.8	**4.5***	**9.3***	
		LAIJ: 19 (4.3)	---	57 (13.6)	75 (17.3)	---	**9.3***	**13.0***	
Sustained Pain Freedom – at 48 hours	n (%) Sustained pain freedom: headache pain free 2 and 48 hours after first dose, without using any medications after first dose.	301: 42 (7.6)	---	84 (14.9)	91 (16.4)	---	**7.3***	**8.8***	
		302: 68 (11.8)	89 (14.9)	86 (15.1)	111 (19.6)	3.1	3.3	**7.8***	
		LAIJ: 19 (4.3)	---	39 (9.3)	67 (15.4)	---	**5.0***	**11.1***	

Table 57 Unfavourable Effects Table of Lasmiditan for Use in the Acute Treatment of Migraine with or without Aura in Adults

Effect	Short Description	PBO	LTN 50 mg	LTN 100 mg	LTN 200 mg	L50–PBO(%)	L100–PBO(%)	L200–PBO(%)	ALPZ	Strengths / Uncertainties / Limitations
Unfavourable Effects										
Simulated SDLP – At 90 minutes, Study LAHG	Mean in cm (SD)	28.77 (6.73)	38.52 (12.39)	44.03 (13.55)	50.24 (13.76)				1 mg: 51.48 (14.47)	• CNS depressant effects were shown, which translate into typical most common TEAEs (dizziness, somnolence, fatigue), propensity to drug abuse, and driving impairment. However, TEAEs were mild to moderate in severity (>95%), and of short duration. • Changes in vital signs relate to the period 1-2 hours post dose for increases in SBP and up to 4 hours for decrease in pulse rate. • During the long-term Study 305, in which 19.879 migraine attacks
	Diff.: LS means, DRUG–PBO (95% CI)[b] Simulated SDLP: measured by cm of SD from lateral position (LP) at 90 min post-dose					**9.86*** (7.39, 12.33)	**15.35*** (12.87, 17.82)	**21.06*** (18.60, 23.52)	**22.71*** (20.23, 25.18)	
Simulated SDLP –	Mean in cm (SD)	29.90 (6.43)	---	31.21 (6.73)	31.45 (6.42)					

Effect	Short Description	PBO	LTN 50 mg	LTN 100 mg	LTN 200 mg	L50–PBO(%)	L100–PBO(%)	L200–PBO(%)	ALPZ	Strengths / Uncertainties / Limitations
At 8 hours, Study LAIF	Diff.: LS means, LTN–PBO (95% CI)[b] Simulated SDLP: measured by cm of SD from lateral position (LP) at 8 hr post-dose					---	0.98 (-0.43, 2.39)	1.76 (0.32, 3.20)	---	were assessed for up to 1 year, no new safety concerns were observed. • The frequency of TEAEs declines with progressive number of attacks that were treated in the individual patient's history • Rare cases of critical liver enzyme elevations
Drug Liking score Study LAHB	Drug Liking score Study LAHB	53.0	---	68.6	73.3				2 mg: 85.4	• Significantly higher Drug Liking scores than placebo in recreational drug users. However, LTN's abuse liability did not translate into incidences of discrepancies related to missing medication (drug accountability), drug diversion, pertinent overdose, or withdrawal after repetitive dosing in HV
	Diff.: LS means, Drug–PBO (95% CI) Emax of the Drug Liking score on Drug Effects VAS in recreational polydrug users					---	**15.6*** (11.7, 19.6)	**20.3*** (16.6, 24.3)	**32.4*** (28.4, 36.4)	

Abbreviations: ALPZ = alprazolam; CI = confidence interval; Diff. = difference; Emax = maximum effectiveness;301 = Study 301/LAHJ; 302 = Study 302/LAHK; LAIJ = Study LAIJ; LS = least squares; LTN = lasmiditan; MBS = most bothersome symptom; N = number of patients in the given treatment group with data for given analysis; n = number of patients with the specified event; N/A = not available; PBO = placebo; SDLP = standard deviation of lateral position; TEAE = treatment-emergent adverse event, meaning events that occur within 48 hours after the first dose regardless of whether a second dose was taken; VAS = visual analogue scale.

[a] **Bold text** with asterisk * indicates that the difference from placebo was statistically significant at p<.05.
[b] **Bold text** with asterisk * indicates that the upper limit of the 95% CI for the increase in SDLP with lasmiditan versus placebo exceeded the a priori non-inferiority margin of 4.4 cm.
Note: Total N for Phase 2/3 Pool for each treatment group: PBO = 2061, for LTN 50 mg = 824, for LTN 100 mg = 2040, and for LTN 200 mg = 1997
References: Ferrari et al. 2002; Cameron et al. 2015; Simen et al. 2015; Rudisill et al. 2016

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Lasmiditan is a high-affinity (Ki of 1.85 nM), centrally penetrant, selective human serotonin 1F (5-HT1F) receptor agonist that is believed to exert its therapeutic effects in the treatment of migraine by decreasing neuropeptide release and inhibiting pain pathways at the trigeminal nerve.

A sound and comprehensive analysis of clinical trial data was provided to characterize the pharmacology, efficacy, and safety profile of lasmiditan as an acute treatment for migraine attacks. The three pivotal randomized, placebo-controlled trials (301, 302, LAIJ) were designed concordant with IHS and EMA guidance and provide a sound database demonstrating evidence for the benefit of lasmiditan 50 mg, 100 mg, and 200 mg in acute migraine treatment across multiple measures of efficacy. Given the chosen target population and baseline characteristics of included subjects, clinical data generated for lasmiditan are considered representative and transferable to the general episodic migraine population in clinical practice. All 3 studies showed statistically significant effects on multiplicity-controlled analyses of their primary (pain freedom at 2 hours post-dose) and key secondary endpoints (MBS freedom at 2 hours post-dose) across all doses tested.

In study LAIJ, consistency of effect was shown across multiple attacks. Maintenance of effect was shown in open label study 305 providing supportive long-term data for intermittent use of LTN (100 mg, 200 mg) in acute migraine attacks over 1-year. Throughout the entire clinical programme response rates for the various endpoints generally increased with the lasmiditan dose.

One weakness of the overall database lies in the fact that the 50 mg dose arm was not included in study 301 and that no controlled data for consistency of effect (study LAIJ) resp. maintenance of effect (study 305) were provided for the LTN 50 mg dose. In line with the general dose response that was observed along efficacy endpoints, the onset of action was later for the 50 mg dose as compared to the higher doses and superiority over placebo could not be shown for the 50 mg dose in terms of sustained pain freedom over 24 resp. 48 hours.

The clinical safety profile of lasmiditan in the acute treatment of migraine attacks was thoroughly and comprehensively characterised in the dossier. By the entirety of available data, the safety profile of CNS active, selective 5-HT1F receptor agonist lasmiditan is considered rather favourable. Lasmiditan was generally well tolerated in large phase 3 RCTs. Some degree of CNS depressant effects was shown, which translate into typical most common TEAEs (dizziness, somnolence, fatigue), propensity to drug abuse and driving impairment. Changes in vital signs were observed in clinical pharmacology trials. They relate to the period of 1-2 hours post-dose for increases in SBP (2.65 mm Hg) and up to 4 hours post-administration for decreases in pulse rate (approx. -5 and -10 bpm following doses of 50 to 200 mg lasmiditan).

3.7.2. Balance of benefits and risks

Clinically relevant benefits in the acute treatment of migraine attacks were shown for lasmiditan. The risks associated with lasmiditan use are adequately addressed in the product information.

3.8. Conclusions

The overall benefit/risk balance of RAYVOW is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of RAYVOW is favourable in the following indication:

RAYVOW is indicated for the acute treatment of the headache phase of migraine attacks, with or without aura in adults.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

N/A

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lasmiditan is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

5. Appendix

5.1. CHMP AR on New Active Substance (NAS) dated 23 June 2022