REYVOW® (lasmiditan) C-V Demonstrated Pain Freedom from Migraine Attacks At 60 Minutes and Up to 48 Hours in New Phase 3 Study

September 11, 2020

- REYVOW Showed Significant Therapeutic Gains of 17-21% for Pain Freedom at 2 Hours and Met All 18 Gated Endpoints

INDIANAPOLIS, Sept. 11, 2020 /PRNewswire/ -- Adults who took REYVOW® (lasmiditan) C-V for their migraine attacks at doses of 100 mg or 200 mg had 3.8 and 4.6 times greater odds, respectively, of achieving pain freedom at 2 hours compared to those taking placebo (co-primary endpoint), according to results from the recently completed Phase 3 study CENTURION. Additionally, Eli Lilly and Company's (NYSE: LLY) REYVOW demonstrated superiority over placebo in all gated endpoints, including proportions of study participants who after treating their first migraine attack reported pain freedom at 1 hour (200 mg dose), pain relief at 1 hour and 2 hours (both doses), sustained pain freedom at 24 hours (both doses) and 48 hours (200 mg dose), and no disability at 2 hours (both doses). These results are being presented virtually at the PAINWeek® 2020 Live Virtual Conference, Sept. 11-13.

"For the 30 million adults in the U.S. living with migraine attacks, this debilitating neurologic disease often disrupts daily activities and sidelines them in moments that matter," said Mark Mintun, M.D., vice president of pain and neurodegeneration, Eli Lilly and Company. "We are delighted that REYVOW met all 18 patient-centric endpoints. These new clinical insights into REYVOW's efficacy should enable healthcare providers to have more meaningful conversations with people with migraine who seek freedom from their painful attacks."

The CENTURION study assessed REYVOW's efficacy and safety, including consistency of response, in the acute treatment of migraine for adults, with or without aura, across four attacks. In the trial, 1,471 people with migraine were randomized and received at least one dose of either REYVOW 200 mg (n=486), REYVOW 100 mg (n=485) or control treatment (placebo for some but not all attacks, n=500) per attack. Study participants treated a migraine attack when their pain was at least of moderate severity and within 4 hours after pain onset. Co-primary efficacy endpoints included pain freedom at 2 hours for the first attack and pain freedom at 2 hours for 2 of 3 attacks. Secondary endpoints included pain freedom at 60 minutes, sustained pain freedom at 24 and 48 hours, and pain relief at 1 hour and 2 hours, among others. Patients entered results into an electronic diary at 30 minutes, 60 minutes, as well as 2, 4, 6, 24 and 48 hours after dosing. All of the study's treatment comparisons were prespecified and 18 endpoints were gated, meaning they were set before the study ended and each comparison was reviewed separately in a specified order to verify the accuracy of the study results.

REYVOW SUPERIORITY COMPARED TO PLACEBO IN PAIN FREEDOM

Pain freedom is defined as a reduction of pain at baseline to no pain.

Pain Freedom Outcomes at 2 Hours and at 60 Minutes

Study results show that people receiving REYVOW 200 mg had 4.6 times greater odds of achieving pain freedom at 2 hours (co-primary endpoint) than those on placebo (29.3% vs. 8.4%; odds ratio: 4.6; p<0.001), with a therapeutic gain of approximately 21%. Study participants taking REYVOW 100 mg had 3.8 times greater odds of achieving pain freedom at 2 hours than those on placebo (25.8% vs. 8.4%; p<0.001), with a therapeutic gain of approximately 17%. These therapeutic gains capture the differences between REYVOW and placebo groups in the percentages of patients who were pain-free at 2 hours. At 60 minutes, people who took REYVOW 200 mg had 7 times greater odds of achieving pain freedom than those on placebo (12.7% vs. 2.0%; p<0.001). Although not a gated endpoint, 6.0% of people receiving REYVOW 100 mg were pain-free at 1 hour vs. 2.0% on placebo.

Sustained Pain Freedom Outcomes at 24 and 48 Hours

Study participants receiving REYVOW 200 mg had 4.7 times greater odds to reach sustained pain freedom at 24 hours than those on placebo (17.3% vs. 4.3%), and those receiving REYVOW 100 mg had 3.5 times greater odds compared to placebo (13.6% vs. 4.3%; p<0.001 each). People receiving REYVOW 200 mg had 4.1 times greater odds of achieving sustained pain freedom at 48 hours than those receiving placebo (15.4% vs. 4.3%; p<0.001). Although not a gated endpoint, 9.3% of people taking REYVOW 100 mg had sustained pain freedom at 48 hours, compared to 4.3% for placebo.

"Migraine attacks affect patients in different ways, so it's important patients have options to help achieve their individual treatment goals," said study investigator and co-author Uwe Reuter, M.D., Ph.D., professor of neurology, Charite University Hospital of Berlin, Berlin, Germany. "I'm encouraged by this study, in which we saw REYVOW helped patients be pain-free in as early as 60 minutes and for up to 48 hours."

REYVOW SUPERIORITY COMPARED TO PLACEBO IN PAIN RELIEF, NO DISABILITY AND GROUP WITH PRIOR TRIPTAN HISTORY

Pain relief is defined as headache pain that reduced to mild or resolved completely.

Pain Relief Outcomes at 2 Hours and at 60 Minutes

Nearly two-thirds of people on REYVOW reported pain relief at 2 hours, 65.2% and 65.4% for REYVOW 200 mg and 100 mg, respectively, compared to 41.3% taking placebo (p<0.001 for each comparison). At 60 minutes, almost half of participants on REYVOW achieved pain relief, 47.2% for those taking REYVOW 200 mg and 48.7% for those on REYVOW 100 mg, compared to 29.3% for those on placebo (p<0.001 each).

Disability Outcomes at 2 Hours and Group with Prior Triptan History Outcomes at 2 Hours

When patients were asked whether their migraine interfered with daily activities at 2 hours after treatment, nearly one in five of those taking REYVOW

reported that no longer was the case (19.8% for 200 mg dose and 18.6% for 100 mg dose), approximately twice the proportion of people on placebo (9.5%; p<0.001 for each REYVOW comparison to placebo).

For study participants who had previously tried triptans that proved ineffective, intolerable or became contraindicated in treating their migraine attacks (n=579), close to three times as many people on REYVOW were pain-free at 2 hours (24.0% for 100 mg dose and 25.6% for 200 mg dose), compared to those taking placebo (8.8%; p<0.001 for each REYVOW comparison to placebo).

"In this study, participants who took REYVOW experienced superior results for pain freedom, pain relief, freedom from disability, and other important treatment outcomes after their first migraine attack compared to those who took a placebo," said study investigator and co-author Timothy R. Smith, M.D., RPh, president and CEO of StudyMetrix Research. "This analysis is exciting, considering so many people need help treating their debilitating migraine attacks, which often interfere with everyday moments."

SAFETY FINDINGS

Observed safety findings in the CENTURION study were generally consistent with those seen in previous REYVOW clinical trials. The incidence of serious treatment-emergent adverse events (TEAEs) during the study was similar across treatment arms: REYVOW 200 mg [n=2 (0.4%)], REYVOW 100 mg [n=1 (0.2%)] and placebo [n=2 (0.4%)]. The most frequent TEAEs seen after treatment for the first attack for REYVOW (≥2% in either dose group in the first attack) included dizziness, paresthesia (tingling), fatigue, nausea, vertigo (sensation of spinning or movement), somnolence (sleepiness), hypoesthesia (diminished sensation), muscle weakness, asthenia (abnormal physical weakness) and feeling abnormal.

"We are thrilled about the REYVOW insights from the robustly designed CENTURION study, including the significant therapeutic gains seen for pain freedom at 2 hours, and look forward to sharing consistency results next month at the virtual 18th Migraine Trust International Symposium (MTIS 2020), Oct. 3-9," said Patrik Jonsson, senior vice president and president of Lilly Bio-Medicines. "This is meaningful for healthcare providers and their patients when making important treatment decisions for migraine attacks."

ABOUT REYVOW® (lasmiditan) TABLETS

REYVOW is a novel oral medication that strongly binds to 5-HT_{1F} receptors located both centrally and peripherally, which may play a role in migraine, a neurologic disease. REYVOW is approved for the acute treatment of migraine with or without aura in adults and is not indicated for the prevention of migraine. REYVOW, the first and only FDA-approved ditan, is brain-penetrant and presumably exerts its therapeutic effects by activating these receptors; however, the precise mechanism is unknown.

IMPORTANT SAFETY INFORMATION FOR REYVOW

WARNINGS AND PRECAUTIONS

Driving Impairment

REYVOW may cause significant driving impairment. In a driving study, administration of single 50 mg, 100 mg, or 200 mg doses of REYVOW significantly impaired subjects' ability to drive. Additionally, more sleepiness was reported at 8 hours following a single dose of REYVOW compared to placebo. Advise patients not to engage in potentially hazardous activities requiring complete mental alertness, such as driving a motor vehicle or operating machinery, for at least 8 hours after each dose of REYVOW. Patients who cannot follow this advice should not take REYVOW. Prescribers and patients should be aware that patients may not be able to assess their own driving competence and the degree of impairment caused by REYVOW.

Central Nervous System Depression

REYVOW may cause central nervous system (CNS) depression, including dizziness and sedation. Because of the potential for REYVOW to cause sedation, other cognitive and/or neuropsychiatric adverse reactions, and driving impairment, REYVOW should be used with caution if used in combination with alcohol or other CNS depressants. Patients should be warned against driving and other activities requiring complete mental alertness for at least 8 hours after REYVOW is taken.

Serotonin Syndrome

In clinical trials, reactions consistent with serotonin syndrome were reported in patients treated with REYVOW who were not taking any other drugs associated with serotonin syndrome. Serotonin syndrome may also occur with REYVOW during coadministration with serotonergic drugs [e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and monoamine oxidase (MAO) inhibitors]. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular signs (e.g., hyperreflexia, incoordination), and/or gastrointestinal signs and symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue REYVOW if serotonin syndrome is suspected.

Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamines, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (i.e., medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients including withdrawal of the overused drugs and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

ADVERSE REACTIONS

The most common adverse reactions associated with REYVOW (≥2% and greater than placebo in clinical studies) were dizziness, fatigue, paresthesia, sedation, nausea and/or vomiting, and muscle weakness.

DRUG ABUSE AND DEPENDENCE

REYVOW contains lasmiditan, a Schedule V controlled substance.

Abuse

In a human abuse potential study in recreational poly-drug users (n=58), single oral therapeutic doses (100 mg and 200 mg) and a supratherapeutic dose (400 mg) of REYVOW were compared to alprazolam (2 mg) (C-IV) and placebo. With all doses of REYVOW, subjects reported statistically significantly higher "drug liking" scores than placebo, indicating that REYVOW has abuse potential. Subjects who received REYVOW reported

statistically significantly lower "drug liking" scores than alprazolam. Euphoric mood occurred to a similar extent with REYVOW 200 mg, REYVOW 400 mg, and alprazolam 2 mg (43-49%). A feeling of relaxation was noted in more subjects on alprazolam (22.6%) than with any dose of REYVOW (7-11%). Phase 2 and 3 studies indicate that, at therapeutic doses, REYVOW produced adverse events of euphoria and hallucinations to a greater extent than placebo. However, these events occur at a low frequency (about 1% of patients). Evaluate patients for risk of drug abuse and observe them for signs of lasmiditan misuse or abuse.

Dependence
Physical withdrawal was not observed in healthy subjects following abrupt cessation after 7 daily doses of lasmiditan 200 mg or 400 mg.

See **Full Prescribing Information and Medication Guide.**

LM HCP ISI 11JAN2020

About Migraine

Migraine is a severely disabling neurologic disease characterized by recurrent episodes of moderate to severe headache accompanied by other symptoms including nausea, sensitivity to light, and sensitivity to sound. More than 30 million American adults have migraine, with three times more women than men affected by migraine. Migraine is often incapacitating, leading to high personal, societal and economic burden. According to the Medical Expenditures Panel Survey, total annual healthcare costs associated with migraine are estimated to be as high as $56 billion in the United States, yet it remains under-recognized and under-treated.

About Lilly's Commitment to Headache Disorders
For over 25 years, Lilly has been committed to helping people affected by headache disorders, investigating more than a dozen different compounds for the treatment of migraine and cluster headache. These research programs have accelerated our understanding of these diseases and furthered the advancement of treatments for headache disorders including REYVOW, approved by the FDA for the acute treatment of migraine, with or without aura, in adults. Our goal is to apply our combined clinical, academic and professional experience to build a research portfolio that delivers broad solutions and addresses the needs of people affected by these disabling neurologic diseases.

About Eli Lilly and Company

Lilly is a global health care leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom. P-LLY

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about REYVOW (lasmiditan) as a treatment for patients with migraine and reflects Lilly's current beliefs. Among other things, there is no guarantee that future study results will be consistent with study findings to date, that REYVOW will receive additional regulatory approvals, or that REYVOW will be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

Refer to: Jen Dial; dial_jennifer_kay@lilly.com; 317-220-1172 (Lilly Bio-Medicines)
Kevin Hern; hern_kevin_r@lilly.com; 317-277-1838 (Investor Relations)

View original content to download multimedia:http://www.prnewswire.com/news-releases/reyvow-lasmiditan-c-v-demonstrated-pain-freedom-from-migraine-attacks-at-60-minutes-and-up-to-48-hours-in-new-phase-3-study-301127830.html

SOURCE Eli Lilly and Company