REYVOW® (lasmiditan) C-V Demonstrated Superior Pain Freedom At 2 Hours in At Least 2 of 3 Migraine Attacks in New Phase 3 Consistency of Effect Study

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Patients on REYVOW had 3.8-7.2 Times Greater Odds of Achieving Pain Freedom at 2 Hours Versus Placebo in At Least 2 out of 3 Attacks, Resulting in Significant Therapeutic Gains of 10-20%

INDIANAPOLIS, Oct. 6, 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 7.2 times greater odds, respectively, of achieving superior pain freedom at 2 hours post treatment compared to those taking placebo in at least 2 out of 3 attacks (co-primary endpoint), new findings from the recently completed Phase 3 study CENTURION reveal. This co-primary endpoint result translated to therapeutic gains, or differences between REYVOW and placebo groups, of approximately 10-20%. Moreover, in at least 2 out of 3 attacks, Eli Lilly and Company's (NYSE: LLY) REYVOW demonstrated superiority over placebo in pain relief at 2 hours. In addition, significantly more study participants who treated their migraine attacks with REYVOW achieved pain freedom and pain relief at 2 hours in 2 out of 3 attacks with REYVOW versus those on placebo, even if they had previously tried triptans that were ineffective, intolerable or became contraindicated. As previously reported, REYVOW demonstrated superiority over placebo in all of the study's 18 gated endpoints. Study investigator Dr. Messoud Ashina, M.D., professor of neurology, Danish Headache Center and Dept. of Neurology, University of Copenhagen, Copenhagen, Denmark and Dr. Uwe Reuter, M.D., Ph.D., professor of neurology, Charite University Hospital of Berlin, Berlin, Germany, are presenting these results and answering questions virtually at the 18th Migraine Trust International Symposium (MTIS 2020), during a session on Oct. 7th, 4:45 – 5:45 p.m. CEDT/10:45 – 11:45 a.m. EDT.

"Healthcare professionals, advocacy groups and people with migraine have made it clear that one of the most important things they want from an acute treatment is consistent efficacy during the first and subsequent attacks," said Mark Mintun, M.D., vice president of pain and neurodegeneration, Eli Lilly and Company. "Not being able to rely on their migraine treatment causes frustration and disappointment when their medicine doesn't work consistently. We are excited about the latest findings from the CENTURION trial. We believe that REYVOW's therapeutic gain of up to 20% and up to 7.2 times greater odds of achieving pain freedom at 2 hours in at least 2 out of 3 attacks with the 200 mg dose are meaningful for patients and healthcare providers who seek consistency as a goal with acute medications when treating migraine 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 treated with 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. This international trial included patients from Austria, Belgium, China, Czechia, Denmark, France, Germany, Hungary, India, Italy, Mexico, Netherlands, Russian Federation, Spain, Switzerland, United Kingdom and the United States of America. Co-primary efficacy endpoints were pain freedom at 2 hours for the first attack, and pain freedom at 2 hours for at least 2 of 3 attacks. Secondary endpoints included pain relief at 2 hours after the first attack and in at least 2 of 3 attacks and findings in the subset of study participants who had previously tried triptans that were ineffective, intolerable or became contraindicated in treating their migraine attacks. 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.

CONSISTENCY OF PAIN FREEDOM AND PAIN RELIEF AT 2 HOURS

Pain freedom and pain relief, respectively, are defined as a reduction of pain at baseline to no pain, and headache pain that reduced to mild or resolved completely.

Study results show that people taking REYVOW 200 mg had 7.2 times greater odds of achieving pain freedom at 2 hours in at least 2 of 3 migraine attacks (co-primary endpoint) than those on placebo (24.4% vs. 4.3%; odds ratio: 7.2; $p<0.001$), with a therapeutic gain of approximately 20%. People who took REYVOW 100 mg had 3.8 times greater odds of achieving pain freedom at 2 hours in at least 2 of 3 attacks than study participants on placebo (14.4% vs. 4.3%; $p<0.001$), translating to a therapeutic gain for patients taking REYVOW of approximately 10%.

Nearly 2 out of 3 people taking REYVOW achieved pain relief at 2 hours in at least 2 of 3 attacks, including 66.7% and 62.3% of those taking REYVOW 200 mg and 100 mg, respectively, compared to 36.9% of those on placebo ($p<0.001$ for each REYVOW comparison to placebo).

CONSISTENCY OF PAIN FREEDOM AND PAIN RELIEF AT 2 HOURS IN GROUP WITH PRIOR TRIPTAN HISTORY

The study also assessed pain freedom and pain relief at 2 hours in at least 2 of 3 migraine attacks in subsets of participants who had previously tried triptans that were ineffective, intolerable or became contraindicated. These outcomes were non-gated secondary endpoints.

Significantly greater proportions of people taking REYVOW were pain-free at 2 hours in at least 2 of 3 migraine attacks (20.1% for REYVOW 200 mg and 11.0% for REYVOW 100 mg), compared to placebo (4.3%) ($p<0.001$ for each REYVOW comparison to placebo). Nearly 2 out of 3 persons taking REYVOW 200 mg (62.7%) and more than half of participants taking 100 mg (55.6%) achieved pain relief at 2 hours in at least 2 of 3 migraine attacks compared to 1 out of 3 patients (33.6%) on placebo ($p<0.001$ for each REYVOW comparison to placebo).

"In this study, people taking REYVOW, who had previously tried triptans that were ineffective, intolerable or contraindicated, achieved significantly greater pain freedom and pain relief at 2 hours across multiple attacks compared to those taking placebo," said Dr. Ashina. "These latest findings are encouraging news for patients and their healthcare providers when discussing personalized treatment goals such as consistency of response. Migraine attacks can be debilitating so it's imperative patients have acute treatment options that can help them achieve the outcomes that matter to

them."

SAFETY FINDINGS

Observed safety findings in the CENTURION study were generally consistent with those seen in previous REYVOW clinical trials. The most frequent treatment-emergent adverse events (TEAEs) seen for REYVOW (≥2% in either dose group) over all four attacks were 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. The incidence of TEAEs was highest during the first attack.

"Among recently approved novel medications for the acute treatment of migraine, REYVOW is the first and only to be evaluated in a consistency study. Additionally, CENTURION is one of the only studies of an FDA-approved acute treatment for migraine to compare the consistency of efficacy against placebo," said Ilya Yuffa, president of Lilly Bio-Medicines. "We are delighted that REYVOW demonstrated consistent and superior efficacy across multiple migraine attacks compared to placebo. These are meaningful insights for patients and their healthcare providers, and we look forward to sharing the findings with health regulatory authorities in Europe, Japan and China."

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 preventive treatment 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.**

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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.

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SOURCE Eli Lilly and Company