Lancet Neurology Publishes Positive, Pivotal Phase 3 Data of Xywav® (calcium, magnesium, potassium, and sodium oxybates) Oral Solution for Idiopathic Hypersomnia

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Treatment with Xywav resulted in clinically meaningful improvement in idiopathic hypersomnia symptoms, including excessive daytime sleepiness, sleep inertia and prolonged sleep duration with an overall safety profile consistent with other oxybate studies

Trial results supported the U.S. FDA approval of Xywav for idiopathic hypersomnia in August 2021, making it the first and only treatment approved for patients living with the debilitating and chronic sleep disorder

DUBLIN, Jan. 5, 2022 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced positive data from the Phase 3 multicenter, placebo-controlled, double-blind, randomized withdrawal study of Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution for the treatment of adults with idiopathic hypersomnia were published online in *The Lancet Neurology*.

The results of the Phase 3 clinical trial showed clinically meaningful and statistically significant differences with *Xywav* compared to placebo in the primary endpoint of change in the Epworth Sleepiness Scale (ESS) score and key secondary endpoints, which included measures that assessed patients' perceptions of the changes in their idiopathic hypersomnia overall (PGIc), symptom severity, including excessive daytime sleepiness (EDS), sleep inertia and prolonged sleep duration (Idiopathic Hypersomnia Severity Scale), and improved daytime performance.[1] In August 2021, *Xywav* became the first and only drug approved for patients with idiopathic hypersomnia by the U.S. Food and Drug Administration (FDA).[2] *Xywav* for idiopathic hypersomnia was made commercially available in November 2021.

"The full data set from the largest global Phase 3 trial in adults with idiopathic hypersomnia represents a major advance in this condition and will enable physicians to make more informed, evidence-driven treatment decisions," said Yves Dauvilliers, M.D., Ph.D., lead investigator of the study and director of the Sleep and Wake Disorders Centre in the Department of Neurology at the Gui de Chauliac Hospital in Montpellier, France. "The trial results demonstrate that *Xywav* offers significant and clinically meaningful improvements to multiple aspects of this debilitating condition that can benefit the sleep and daily lives of adults diagnosed with this unique sleep disorder."

Additionally, the FDA has recognized seven years of Orphan Drug Exclusivity for *Xywav* for the treatment of idiopathic hypersomnia in adults. The FDA's Orphan Drug Designation program is designed to advance the development of drugs that treat a condition affecting 200,000 or fewer U.S. patients annually. The seven-year market exclusivity for *Xywav* for idiopathic hypersomnia began on August 12, 2021, the date of FDA approval for this indication. In June 2021, the FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years and older with narcolepsy.

Idiopathic hypersomnia is a debilitating neurologic sleep disorder characterized by chronic excessive daytime sleepiness, which is the inability to stay awake and alert during the day resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness. Core symptoms of idiopathic hypersomnia may include confusion, irritability and severe sleep inertia or sleep drunkenness (prolonged difficulty in waking up with frequent reentries into sleep). In addition, people with idiopathic hypersomnia may experience prolonged, non-restorative nighttime sleep, cognitive impairment in thinking, and long and unrefreshing naps.[3,4,5,6]

"*Xywav* is the only FDA-approved medicine available to treat idiopathic hypersomnia, providing clinicians with an effective and meaningful option for their patients to help relieve symptoms like sleep inertia and excessive daytime sleepiness," said Rob Iannone, M.D., M.S.C.E., executive vice president, research and development and chief medical officer of Jazz Pharmaceuticals. "We are committed to addressing the debilitating unmet needs of patients with neurological disorders through the development of novel medicines that can transform lives, and our launch of *Xywav* for use in idiopathic hypersomnia is one example of Jazz's evolved R&D capabilities."

Phase 3 Trial Results

In the trial (NCT03533114), investigators at 50 centers in seven countries enrolled a total of 154 adults aged 19 to 75 diagnosed with idiopathic hypersomnia. Following a screening period, the study had three dosing periods. First, participants received open-label *Xywav* for 10 to 14 weeks, until their individual doses were optimized. Optimized dose ranged from 2.5 to 9.0 grams per night. Patients then received stable, optimized doses for two weeks, with median doses of 4.5 ((interquartile range [IQR], (3.0 to 5.0) grams nightly (one dose regimen, 21 patients) and 7.5 (IQR 6.5 to 8.1) grams nightly (two-dose regimen, 93 patients), with 40 patients changing dosing regiments once or more times. During a double-blind randomized withdrawal period (DBRWP), patients received either the optimized stable dose of *Xywav* or a placebo for two weeks.[1]

Participants entered the study with a mean (SD) ESS score of 16.1 (3.6), indicating substantial excessive daytime sleepiness. During the *Xywav* open-label titration and optimization period, ESS scores decreased, indicating improvement, which was maintained during the stable dose period (SDP).

The study's primary endpoint was change in the ESS scores as measured from the end of the SDP to the end of the DBRWP. Participants randomized to continue *Xywav* had stable mean (SD) ESS scores [from 6.3 (4.3) to 7.0 (5.0)], in contrast to those randomized to placebo whose mean (SD) ESS scores increased from 5.8 (3.7) to 13.3 (4.1) points, indicating worsening. The differences between the two group's mean ESS scores, [5.8 (3.7) to 13.3 (4.1)] were statistically significant, [95% CI: -6.5 points (-8.0, -5.0), P<0.0001].[1] An ESS score of below 10 is considered normal among those without a sleep disorder.

Participants entered the study with a mean (SD) IHSS score of 32.1 (8.0) indicating severe disease. During the *Xywav* open-label titration and optimization period, IHSS scores decreased, indicating improvement, which was maintained during the SDP. On the key secondary endpoint, participants randomized to continue *Xywav* had stable mean IHSS scores (15.5 [9.2] to 16.9 [8.1]), in contrast to those randomized to placebo whose

mean (SD) IHSS scores increased from (15.2 [7.8] to 28.5 [9.0]), indicating worsening. The difference in change in IHSS score was statistically significant (estimated median difference [95% CI: -12.0 (-15.0, -8.0); P<0.0001]. A score of 22 or below is considered the best cutoff to differentiate individuals with untreated idiopathic hypersomnia from a control population without sleepiness.[7]

Xywav also demonstrated clinically meaningful differences compared to placebo on the Patient Global Impression of Change (PGIc) [difference in proportion worsened, 95% CI: -67 (-80%, -53%; P<0.0001],[1] as well as four other secondary endpoints that documented the benefits of *Xywav* vs. placebo, including the Clinical Global Impression of Change (CGIc), the Functional Outcomes of Sleep Questionnaire, short version (FOSQ-10), the visual analog scale for sleep inertia (VAS-SI) and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP). The distribution of ratings by investigators using the CGIc scale demonstrated worsening in symptoms among fewer participants randomized to *Xywav* compared to those on placebo, indicating clinical satisfaction with the treatment. Also, a difference in the median scores were observed in the *Xywav* group vs. the placebo group, on the FOSQ-10 [95% CI: 3.7 (2.5, 5.0), nominal P<0.0001]. Participants' VAS-SI scores decreased, indicating an improvement, from the last week of screening to the end of the SDP, then remained stable during DBRWP in the group randomized to *Xywav* and increased in the placebo group [least squares mean difference 95% CI: −22.2 (−29.7, −14.8), nominal P<0.0001].

On the WPAI:SHP, significant differences between the groups from end of SDP to end of DBRWP were observed with estimated median differences of [95% CI: 0.0 (−3.2, 0), P=0.0092] for absenteeism, [95% CI: -27.5 (-37.1, -17.9, P<0.0001] for presenteeism, [95% CI: −30.8 (−39.9, −21.7), P<0.001] for overall work impairment, and [95% CI: -31.7 (-40.0, -23.5), P<0.0001] for overall activity impairment.[1]

The participants' maintained their improvements in all of the endpoint outcomes from the first day of *Xywav* treatment through the SDP and throughout open label extension, excluding the two-week DBRWP.

Treatment-emergent adverse events (TEAEs) reported by more than 10 percent of the participants in the trial included nausea (22%), headache (18%), dizziness (12%), anxiety (11%), and vomiting (11%). Most participants experienced TEAEs that were mild or moderate. Four participants experienced nine serious TEAEs, none of which were deemed to be related to study drug by the investigator. No deaths occurred during the trial.[1]

Xywav has a Boxed Warning as a central nervous system (CNS) depressant and for its potential for abuse and misuse. Because of the risks of CNS depression and abuse and misuse, *Xywav* is available only through a restricted program called the *Xywav* and *Xyrem* REMS.

Please see the full Prescribing Information, including Boxed Warning, and Medication Guide, is available here. <http://pp.jazzpharma.com/pi/xywav.en.USPI.pdf>

About Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution
Xywav, also known as JZP258, is a lower-sodium oxybate approved by the U.S. Food and Drug Administration (FDA) for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy and for the treatment of idiopathic hypersomnia in adults. FDA recognized seven years of Orphan Drug Exclusivity for *Xywav* in June 2021 for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy, and in December 2021 for the treatment of idiopathic hypersomnia in adults. The Office of Orphan Product Development (OOPD) at the FDA also published its summary of clinical superiority findings for *Xywav* for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy by means of greater safety compared to Xyrem® (sodium oxybate). The decision of the OOPD is based on FDA findings that *Xywav* provides a greatly reduced chronic sodium burden compared to *Xyrem*. There are no head-to-head data for *Xywav* and *Xyrem*. *Xywav* is comprised of a unique composition of cations resulting in 92% less sodium, or a reduction of approximately 1,000 to 1,500 mg/night, than sodium oxybate at the recommended adult dosage range of 6 to 9 grams. While the exact mechanism of action of *Xywav* is unknown, it is hypothesized that the therapeutic effects of *Xywav* on cataplexy and excessive daytime sleepiness are mediated through $GABA_B$ actions during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.[2] The U.S. Drug Enforcement Agency (DEA) has designated *Xywav* as a Schedule III medicine. The DEA defines Schedule III drugs, substances, or chemicals as drugs with a moderate to low potential for physical and psychological dependence.[2,8]

Important Safety Information

WARNING: Taking XYWAV with other central nervous system (CNS) depressants such as medicines used to make you or your child fall asleep, including opioid analgesics, benzodiazepines, sedating antidepressants, antipsychotics, sedating anti-epileptic medicines, general anesthetics, muscle relaxants, alcohol, or street drugs, may cause serious medical problems, including trouble breathing (respiratory depression), low blood pressure (hypotension), changes in alertness (drowsiness), fainting (syncope), and death.

The active ingredient of XYWAV is a form of gamma hydroxybutyrate (GHB). Abuse or misuse of illegal GHB alone or with other drugs that cause changes in alertness (or consciousness) has caused serious side effects. These effects include seizures, trouble breathing (respiratory depression), changes in alertness (drowsiness), coma, and death. Call your doctor right away if you or your child has any of these serious side effects.

Because of these risks, you have to go through the XYWAV and XYREM REMS to have your or your child's prescription for XYWAV filled.

Do not take XYWAV if you take or your child takes other sleep medicines or sedatives (medicines that cause sleepiness), drinks alcohol, or has a rare problem called succinic semialdehyde dehydrogenase deficiency.

Keep XYWAV in a safe place to prevent abuse and misuse. Selling or giving away XYWAV may harm others and is against the law. Tell your doctor if you have ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Anyone who takes XYWAV should not do anything that requires them to be fully awake or is dangerous, including driving a car, using heavy machinery, or flying an airplane, for at least 6 hours after taking XYWAV. Those activities should not be done until you know how XYWAV affects you or your child.

XYWAV can cause serious side effects, including the following:

- **Breathing problems, including** slower breathing, trouble breathing, and/or short periods of not breathing while sleeping

(sleep apnea). People who already have breathing or lung problems have a higher chance of having breathing problems when they use XYWAV.

- **Mental health problems, including** confusion, seeing or hearing things that are not real (hallucinations), unusual or disturbing thoughts (abnormal thinking), feeling anxious or upset, depression, thoughts of killing yourself or trying to kill yourself, increased tiredness, feelings of guilt or worthlessness, or difficulty concentrating. Tell your doctor if you or your child have or had depression or have tried to harm yourself or themselves. **Call your doctor right away if you have or your child has symptoms of mental health problems or a change in weight or appetite.**
- **Sleepwalking**. Sleepwalking can cause injuries. Call your doctor if this occurs.

The most common side effects of XYWAV in adults include nausea, headache, dizziness, anxiety, insomnia, decreased appetite, excessive sweating (hyperhidrosis), vomiting, diarrhea, dry mouth, parasomnia (a sleep disorder that can include abnormal dreams, abnormal rapid eye movement (REM) sleep, sleep paralysis, sleep talking, sleep terror, sleep-related eating disorder, sleep walking, and other abnormal sleep-related events), somnolence, fatigue, and tremor.

The most common side effects of XYREM (which also contains oxybate like XYWAV) in children include nausea, bedwetting, vomiting, headache, weight decrease, decreased appetite, dizziness, and sleepwalking.

XYWAV can cause physical dependence and craving for the medicine when it is not taken as directed. These are not all the possible side effects of XYWAV.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

About Idiopathic Hypersomnia

Idiopathic hypersomnia is an often debilitating, neurologic sleep disorder characterized by chronic excessive daytime sleepiness (the inability to stay awake and alert during the day resulting in the irrepressible need to sleep or unplanned lapses into sleep or drowsiness) that is not caused by other medical, behavioral or psychiatric conditions.[3,4,5,6] Symptoms may also include a prolonged main (nighttime) sleep episode of more than 9 hours or a sleep duration of 11 hours or longer over a 24-hour period, cognitive impairment, long and unrefreshing naps, brain fog, or the inability to focus for long periods of time, and severe sleep inertia (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability).[3,4,5,6,9] Although there are overlapping clinical features with narcolepsy, idiopathic hypersomnia is a condition with its own specific diagnostic criteria.[3,6,10] Idiopathic hypersomnia is a debilitating illness that can significantly affect social, educational and occupational functioning.[11,12] In the U.S., approximately 37,000 adult patients have been diagnosed with idiopathic hypersomnia and are actively seeking healthcare.[14] This low number of people may be due to the many difficulties in identifying and diagnosing idiopathic hypersomnia, as well as distinguishing it from other similar sleep disorders. It is estimated that far fewer patients are currently receiving pharmacological treatment for their idiopathic hypersomnia.[13,14,15,16]

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (NASDAQ: JAZZ) is a global biopharmaceutical company whose purpose is to innovate to transform the lives of patients and their families. We are dedicated to developing life-changing medicines for people with serious diseases—often with limited or no therapeutic options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in neuroscience and oncology. Within these therapeutic areas, we are identifying new options for patients by actively exploring small molecules and biologics, and through innovative delivery technologies and cannabinoid science. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in nearly 75 countries. For more information, please visit www.jazzpharmaceuticals.com and follow @JazzPharma on Twitter.

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