Jazz Pharmaceuticals Announces Positive Top-line Results from Phase 3 Study of Xywav™ (calcium, magnesium, potassium, and sodium oxybates) Oral Solution in Adult Patients with Idiopathic Hypersomnia

October 8, 2020

Clinically meaningful and highly statistically significant results for primary and both key secondary endpoints

U.S. Food and Drug Administration grants Fast Track designation to Xywav for idiopathic hypersomnia, a serious sleep disorder with no approved treatment options

DUBLIN, Oct. 8, 2020 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced positive top-line results from the Phase 3 double-blind, multicenter, placebo-controlled, randomized withdrawal study evaluating the efficacy and safety of an investigational use of Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution in adult patients with idiopathic hypersomnia.

Patients entering the study had excessive daytime sleepiness typical of the idiopathic hypersomnia population. All patients were treated with *Xywav* during the open-label titration period and clinically meaningful improvements in the Epworth Sleepiness Scale (ESS) were observed.

The primary endpoint of ESS and the key secondary endpoints of Patient Global Impression of Change (PGIc) and Idiopathic Hypersomnia Severity Scale (IHSS) were measured during the randomized withdrawal portion of the trial, which included 115 patients. Those who were administered *Xywav* showed clinically meaningful maintenance of efficacy for ESS, PGIc and IHSS, and there were highly statistically significant worsenings in patients administered placebo compared with *Xywav* for ESS (p-value <0.0001), PGIc (p-value <0.0001) and IHSS (p-value <0.0001).

The safety profile in this study was consistent with the known safety profile of *Xywav* with no new safety signals observed in this population.

"We are excited by these compelling results and the magnitude of improvement observed in the study, in particular for people living with idiopathic hypersomnia who currently have no approved treatment option. We are deeply grateful to the patients and investigators who participated in the study, and look forward to working quickly with the FDA to make *Xywav* available to patients as soon as possible," said Robert Iannone, M.D., M.S.C.E., executive vice president, research and development of Jazz Pharmaceuticals. "For more than 15 years, Jazz has been at the forefront of sleep medicine. Our purpose is to innovate to transform the lives of patients and we are committed to bringing new options for people living with serious sleep disorders where there are no or limited treatments available."

Jazz will submit the Phase 3 study data for presentation at an upcoming medical meeting and these data will be included in the planned submission of a supplemental New Drug Application (sNDA) to the FDA as early as the first quarter of 2021. The FDA granted Fast Track designation to *Xywav* in September 2020.

Idiopathic hypersomnia is a chronic, neurological disorder that is characterized by excessive sleepiness, an uncontrollable need to sleep or daytime sleepiness that persists for at least 3 months even with adequate or prolonged nighttime sleep.

"There is significant need for greater awareness of idiopathic hypersomnia, which can severely impact a person's daily life, and can often be mis-diagnosed or undiagnosed over a substantial period of time," said Yves Dauvilliers, MD, Director, Sleep Disorders Centre, Gui de Chauliac Hospital in Montpellier, France and lead investigator of the Phase 3 study. "Currently, there are no approved treatment options for idiopathic hypersomnia, and these data are a welcome advance for patients.[3]"

Xywav was approved in July 2020 by the FDA for the treatment of cataplexy or excessive daytime sleepiness in patients 7 years of age and older with narcolepsy.[1,2] *Xywav* is not currently approved by regulatory authorities for the treatment of idiopathic hypersomnia.

About the Phase 3 Study in Idiopathic Hypersomnia

The Phase 3 study of *Xywav* was a multi-national, double-blind, multicenter, placebo-controlled, randomized withdrawal study evaluating the efficacy and safety of *Xywav* for the investigational treatment of idiopathic hypersomnia in adult patients. The primary endpoint was the change in the ESS score from *Xywav* and placebo over the randomized-withdrawal period. The key secondary endpoints were PGIc and IHSS. IHSS is a recently developed and validated scale, and is a self-report measure of hypersomnolence symptoms, consequences, and responsiveness to treatment.[4]

The study design included a titration and optimization period of up to 14 weeks, a *Xywav* stable-dose period of two weeks, followed by a 1:1 randomization to either *Xywav* or placebo for 2 weeks. After the completion of the double-blind, placebo-controlled treatment period, patients entered a 24-week open-label safety extension period. More information about the study design is available at www.clinicaltrials.gov (identifier: NCT03533114).

About Idiopathic Hypersomnia

Idiopathic hypersomnia is a sleep disorder characterized by chronic and disabling excessive daytime sleepiness (the inability to stay awake and alert during the day resulting in drowsiness and unplanned lapses into sleep) that is not caused by other medical, behavioral or psychiatric conditions known to induce excessive sleepiness.[5,6,7,8] Symptoms may also include prolonged nighttime sleep, long and unrefreshing naps and sleep inertia (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability).[5,6,7,8] Idiopathic hypersomnia is a debilitating illness that can significantly affect social, school and occupational functioning.[8,9] Insurance claims data suggest diagnosed prevalence of IH is approximately 37,000 patients; however, given known mis- and under-diagnoses of IH, in addition to lack of FDA-approved therapies, the unmet need may be significantly greater.

More information about Xywav, including Full Prescribing Information 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 JZP-258, is 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. It is an investigational product candidate being evaluated for the treatment of idiopathic hypersomnia in adult patients. 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.[1]

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 Program 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 you or your child starts sleepwalking. Your doctor should check you or your child.

The most common side effects of XYWAV in adults include headache, nausea, dizziness, decreased appetite, 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), diarrhea, excessive sweating (hyperhidrosis), anxiety and vomiting.

The most common side effects of XYWAV in children include bedwetting, nausea, headache, vomiting, weight decrease, decreased appetite, and dizziness.

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 Jazz Pharmaceuticals plc
Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is a global biopharmaceutical company dedicated to developing life-changing medicines for people with serious diseases — often with limited or no options. We have a diverse portfolio of marketed medicines and novel product candidates, from early- to late-stage development, in key therapeutic areas. Our focus is in neuroscience, including sleep medicine and movement disorders, and in oncology, including hematologic malignancies and solid tumors. We actively explore new options for patients including novel compounds, small molecule advancements, biologics and innovative delivery technologies. Jazz is headquartered in Dublin, Ireland and has employees around the globe, serving patients in more than 90 countries. For more information, please visit www.jazzpharmaceuticals.com and follow @JazzPharma on Twitter.

"Safe Harbor" Statement under the Private Securities Litigation Reform Act of 1995
This press release contains forward-looking statements, including, but not limited to, statements related to the planned sNDA submission to FDA of Xywav for idiopathic hypersomnia and the potential timing of the availability of Xywav for people with idiopathic hypersomnia; and other statements that are not historical facts. These forward-looking statements are based on Jazz Pharmaceuticals' current plans, objectives, estimates, expectations

and intentions and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks and uncertainties associated with: pharmaceutical product development; the regulatory approval process, including the risk that the company may be unable to obtain approval by the FDA of its planned sNDA for Xywav in a timely manner or at all; effectively commercializing Xywav; and other risks and uncertainties affecting the company and its development programs, including those described from time to time under the caption "Risk Factors" and elsewhere in Jazz Pharmaceuticals plc's Securities and Exchange Commission filings and reports (Commission File No. 001-33500), including Jazz Pharmaceuticals' Quarterly Report on Form 10-Q for the quarter ended June 30, 2020 and future filings and reports by Jazz Pharmaceuticals. Other risks and uncertainties of which Jazz Pharmaceuticals is not currently aware may also affect Jazz Pharmaceuticals' forward-looking statements and may cause actual results and the timing of events to differ materially from those anticipated. The forward-looking statements herein are made only as of the date hereof or as of the dates indicated in the forward-looking statements, even if they are subsequently made available by Jazz Pharmaceuticals on its website or otherwise. Jazz Pharmaceuticals undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

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