Jazz Pharmaceuticals Presents Phase 3 Study Results of Xywav™ (calcium, magnesium, potassium, and sodium oxybates) Oral Solution in Adult Patients with Idiopathic Hypersomnia at 2021 American Academy of Neurology Annual Meeting

April 20, 2021

Xywav demonstrated statistically significant differences in change in Epworth Sleepiness Scale score (p-value <0.0001), Patient Global Impression of Change (p-value <0.0001) and the Idiopathic Hypersomnia Severity Scale (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

Company to host investor webcast today at 12:30 p.m. ET

DUBLIN, April 20, 2021 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced positive results from the Phase 3 study of Xywav™ (calcium, magnesium, potassium, and sodium oxybates) oral solution in adult patients with idiopathic hypersomnia, which will be presented during the Clinical Trials Plenary Session of the 2021 American Academy of Neurology (AAN) Annual Meeting between 10:00 a.m. and 12:30 p.m. ET. Jazz will host an investor and analyst presentation via webcast today at 12:30 p.m. ET.

Today's presentation will further quantify the previously reported Phase 3 top-line results. These additional data were submitted to the U.S. Food and Drug Administration (FDA) in the supplemental New Drug Application that was recently accepted for filing and granted Priority Review.

"The efficacy and safety results demonstrate the potential *Xywav* has for people living with idiopathic hypersomnia, a debilitating, chronic sleep disorder for which there are no approved treatments in the U.S.," said Robert Iannone, M.D., M.S.C.E., executive vice president, research and development and chief medical officer of Jazz Pharmaceuticals. "Idiopathic hypersomnia significantly affects the social, educational and occupational functioning of those living with the disorder.[1,2,3,4] We have long understood that sleep disorders can impact every facet of someone's life and are committed to leading the evolution of sleep medicine to offer better therapies."

"The dramatic improvements *Xywav* provided for participants within this study give hope to not only those living with idiopathic hypersomnia, but also to their families, friends and care teams," said Yves Dauvilliers, M.D., director of the Sleep Disorders Centre at the Gui de Chauliac Hospital in Montpellier, France and lead investigator of the Phase 3 study. "People with idiopathic hypersomnia sleep a normal, or longer than normal, amount of sleep each night, but still experience excessive sleepiness during the day.[6,7] If the new indication is approved by the FDA, I believe *Xywav* will make an immediate impact on patients living with idiopathic hypersomnia."

All study participants were treated with *Xywav* during an open-label titration and optimization period of up to 14 weeks (OLT), followed by a two-week, open-label, stable-dose period (SDP). Participants entered the study with a mean (standard deviation; SD) Epworth Sleepiness Scale (ESS) score of 16.1 (3.59), indicating substantial excessive sleepiness. Improvement in ESS score with open-label *Xywav* therapy was observed from a mean of 15.7 (3.77) at study entry to a mean of 6.1 (3.99) at end of SDP.

For Idiopathic Hypersomnia Severity Scale (IHSS), participants entered the study with a mean (SD) IHSS score of 32.1 (7.97), representative of patients with untreated IH. Like ESS, improvement in IHSS score with open-label *Xywav* therapy was observed from a mean of 31.6 (8.34) at study entry to a mean of 15.3 (8.46) at end of SDP.

Participants were then randomized to placebo or to continue *Xywav* during a two-week, double-blind, randomized withdrawal period. The primary endpoint of change in ESS score and the key secondary endpoints of change in IHSS score and proportion of participants who reported worsening on the Patient Global Impression of Change (PGIc) scale were measured during the randomized withdrawal portion of the trial, which included 115 participants.

At the end of the double-blind randomized withdrawal period, participants who were randomized to placebo (n=59) experienced significant worsening compared to those who continued *Xywav* treatment (n=56) in ESS scores LS mean difference [95% CI] in change from SDP to end of DBRWP: −6.51 [−7.99,−5.03]; P<0.0001), PGIc ratings (88.1% vs 21.4% rated minimally/much/very much worse; P<0.0001), and IHSS scores; (estimated median difference [95% CI] in change from end of SDP to end of DBRWP: −12.00 [−15.0,−8.0]; P<0.0001).[5]

The most common treatment-emergent adverse events observed in the study included nausea (21.4%), headache (16.2%), dizziness (11.7%), anxiety (10.4%) and vomiting (10.4%). Four participants reported serious treatment-emergent adverse events, all of which were deemed by the study investigator to not be study drug-related (non-cardiac chest pain, rhabdomyolysis, syncope and nephrolithiasis/pyelonephritis).

Webcast/conference call details

The company will host an audio webcast today at 12:30 p.m. ET to review the Phase 3 idiopathic hypersomnia data being presented at the 2021 AAN Annual Meeting. The live webcast may be accessed from the Investors section of the company's website at www.jazzpharmaceuticals.com. Investors may participate in the conference call by dialing (855) 353-7924 in the U.S. or (503) 343-6056 outside the U.S., and entering passcode 8075156.

An archived version of the webcast will be available for at least one week on the Investors section of the company's website. An audio replay will be available through April 27, 2021 by dialing (855) 859-2056 in the U.S. or (404) 537-3406 outside the U.S., and entering passcode 8075156.

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 an investigational use of *Xywav* in adult patients with idiopathic hypersomnia. Patients entering the study had excessive daytime sleepiness typical of the idiopathic hypersomnia population. 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.[8]

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. More information about the study design is available at www.clinicaltrials.gov (identifier: NCT03533114).

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.[6,7,9,10] Symptoms may also include a prolonged main sleep episode of more than 9 hours or a sleep duration of 11 hours or longer over a 24-hour period, prolonged, non-restorative nighttime sleep and long and unrefreshing naps, and severe sleep inertia (prolonged difficulty waking, with frequent reentries into sleep, confusion, and irritability). [6,7,9,10] Although there are overlapping clinical features with narcolepsy, idiopathic hypersomnia is a condition with its own specific diagnostic criteria.[9,10,11] Idiopathic hypersomnia is a debilitating illness that can significantly affect social, educational and occupational functioning.[1,2,3,4] Insurance claims data suggest the number of people diagnosed with idiopathic hypersomnia and actively seeking healthcare is 37,000 patients in the U.S.; however, given that idiopathic hypersomnia is often misdiagnosed, in addition to the lack of an FDA-approved treatment, many people with idiopathic hypersomnia remain undiagnosed indicating that the unmet need may be significantly greater.[12,13,14,15]

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, potassiumand sodium oxybates) oral solution

Xywav, also known as JZP-258, 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. It is an investigational product 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.[16] *Xywav* received Fast Track designation by the FDA in September 2020 for the treatment of idiopathic hypersomnia.

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 potential timing of the availability of *Xywav* for people with idiopathic hypersomnia and the potential impact on that community; 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 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' Annual Report on Form 10-K for the year ended December 31, 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.

Media Contact:
Jacqueline Kirby, Vice President, Corporate Affairs & Government Relations
Ireland +353 1 697 2141 U.S. +1 215 867 4910

Investor Contact:
Andrea N. Flynn, Ph.D., Vice President, Head, Investor Relations
Ireland +353 1 634 7887 U.S. +1 561 306 4035

References:

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fifth Edition (DSM-5). 2020.
2. Evangelista E, Lopez R, Dauvilliers Y. Update on treatment for idiopathic hypersomnia. *Expert Opin Investig Drugs*. 2018 Feb;27(2):187-192. doi: 10.1080/13543784.2018.1417385. Epub 2018 Jan 3. PMID: 29250981.
3. Ozaki A, Inoue Y, Hayashida K, Nakajima T, Honda M, Usui A, Komada Y, Kobayashi M, Takahashi K. Quality of life in patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time: comparison between patients on psychostimulants, drug-naïve patients and the general Japanese population. *Sleep Med*. 2012 Feb;13(2):200-6. doi: 10.1016/j.sleep.2011.07.014. Epub 2011 Dec 3. PMID: 22137109.
4. Hess G, Mehra R, Carls G, et al. 0625 US Prevalence of Narcolepsy and Other Sleep Disorders From 2013–2016: A Retrospective, Epidemiological Study Utilizing Nationwide Claims. *Sleep*. 2018 Apr;41(suppl_1):A232-A232. doi: 10.1093/sleep/zsy061.624
5. Dauvilliers Y, Evangelista E, Barateau L, Lopez R, Chenini S, Delbos C, Beziat S, Jaussent I. Measurement of symptoms in idiopathic hypersomnia: The Idiopathic Hypersomnia Severity Scale. Neurology. 2019 Apr 9;92(15):e1754-e1762. doi: 10.1212/WNL.0000000000007264. Epub 2019 Mar 13. PMID: 30867266.
6. Trotti LM. Idiopathic Hypersomnia. *Sleep Med Clin*. 2017;12(3):331-344. doi:10.1016/j.jsmc.2017.03.009.
7. American Academy of Sleep Medicine. The International Classification of Sleep Disorders. Third Edition (ICSD-3). 2014.
8. Dauvilliers Y, Evangelista E, Barateau L, et al. Measurement of symptoms in idiopathic hypersomnia: The Idiopathic Hypersomnia Severity Scale. *Neurology*. 2019;92(15):e1754-e1762. doi:10.1212/WNL.0000000000007264.
9. Billiard M, Sonka K. Idiopathic hypersomnia. *Sleep Med Rev*. 2016 Oct;29:23-33. doi: 10.1016/j.smrv.2015.08.007. Epub 2015 Sep 3. PMID: 26599679.
10. Khan Z, Trotti LM. Central Disorders of Hypersomnolence: Focus on the Narcolepsies and Idiopathic Hypersomnia. *Chest*. 2015;148(1):262-273. doi:10.1378/chest.14-1304
11. Jazz Pharmaceuticals, Inc, Data on file. JZP258-2020-047-29 Oct 2020.
12. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. *Sleep*. 2007 Oct;30(10):1274-81. doi: 10.1093/sleep/30.10.1274. PMID: 17969461; PMCID: PMC2266276.
13. Masri TJ, Gonzales CG, Kushida CA. Idiopathic Hypersomnia. *Sleep Medicine Clinics*. 2012 June;7(2):283-289. doi: https://doi.org/10.1016/j.jsmc.2012.03.012
14. Jazz Pharmaceuticals, Inc, Data on file.
15. Trotti LM, Arnulf I. Idiopathic Hypersomnia and Other Hypersomnia Syndromes. *Neurotherapeutics*. 2020 Sep 8. doi:

10.1007/s13311-020-00919-1. Epub ahead of print. PMID: 32901432.
16. Xywav (calcium, magnesium, potassium and sodium oxybates) oral solution Prescribing Information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.

View original content to download multimedia:http://www.prnewswire.com/news-releases/jazz-pharmaceuticals-presents-phase-3-study-results-of-xywav-calcium-magnesium-potassium-and-sodium-oxybates-oral-solution-in-adult-patients-with-idiopathic-hypersomnia-at-2021-american-academy-of-neurology-annual-meeting-301272417.html

SOURCE Jazz Pharmaceuticals plc