



Jazz Pharmaceuticals Presents Positive JZP-258 Phase 3 Study Data at World Sleep 2019

September 25, 2019

JZP-258 achieves primary and key secondary endpoints demonstrating highly statistically significant differences in weekly number of cataplexy attacks and Epworth Sleepiness Scale scores compared to placebo

JZP-258 is a novel oxybate product candidate with a unique composition of cations resulting in 92% less sodium than Xyrem® (sodium oxybate)

DUBLIN, Sept. 25, 2019 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) announced today that positive data from the Phase 3 study of its investigational medicine, JZP-258, for the treatment of cataplexy and excessive daytime sleepiness (EDS) in adults with narcolepsy were presented at World Sleep 2019 in Vancouver, Canada. Data from the study were presented in an oral presentation today at 5:00 p.m. PDT and in a poster presentation on September 24.

"We are pleased with the positive results from the Phase 3 study of JZP-258, which demonstrate the efficacy of JZP-258 for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy," said Jed Black, M.D., senior vice president, Sleep and Neuroscience at Jazz Pharmaceuticals and adjunct professor, Stanford University Medical Center, Stanford Center for Sleep Sciences and Medicine. "These data support the efficacy and overall safety profile of a lower-sodium oxybate formulation for people living with narcolepsy, a chronic condition that may require lifelong therapy. There is broad consensus among health care organizations, like the National Academy of Sciences and American Heart Association, that lowering sodium intake lowers the risk of cardiovascular disease. We believe that JZP-258, if approved, will provide a clinically meaningful benefit to patients prescribed oxybate."

The Phase 3 study of JZP-258 was a global, double-blind, placebo-controlled, randomized-withdrawal, multicenter study evaluating the efficacy and safety of JZP-258 in the treatment of cataplexy and EDS in adults with narcolepsy. The primary endpoint was the change in the weekly number of cataplexy attacks, and the key secondary endpoint was the change in the Epworth Sleepiness Scale (ESS) score with JZP-258 compared to placebo. The study enrolled 201 participants and randomized 134 participants, comprising a heterogeneous population, which included those previously treated with sodium oxybate and naïve to sodium oxybate, with or without other anticataplectic treatments. A randomized-withdrawal study design aims to measure efficacy – specifically, maintenance of effect – for participants who continue on active treatment – and worsening for participants randomized to placebo.

The study design included an optimization and titration period of up to 12 weeks, a JZP-258 stable-dose period of two weeks, followed by 1:1 randomization to either JZP-258 or placebo for two weeks. After the completion of the double-blind, placebo-controlled treatment period, patients had the opportunity to receive JZP-258 in an optional 24 week open-label safety extension period. More information about the study design is available at www.clinicaltrials.gov (identifier: NCT03030599).

During the double-blind withdrawal period, there was a significant increase in median weekly number of cataplexy attacks in participants randomized to placebo compared with participants randomized to JZP-258 (median [Q1, Q3]: 2.35 [0.00, 11.61] vs 0.00 [-0.49, 1.75], respectively; treatment difference, $P < 0.0001$).

As expected, initial cataplexy rates differed based on prior therapy at study entry, with participants taking sodium oxybate only or sodium oxybate and an antidepressant/anticataplectic reporting the least cataplexy at study entry. In participants taking sodium oxybate only at study entry, cataplexy was stable with JZP-258 treatment across the open-label treatment titration and optimization period and the stable dose period (SDP). In those taking sodium oxybate and an antidepressant/anticataplectic at study entry, cataplexy was stable during initial titration of JZP-258, increased during taper and discontinuation of the other anticataplectic, and stabilized during SDP. In participants taking an anticataplectic other than sodium oxybate at study entry, cataplexy decreased during initial titration of JZP-258, increased during taper and discontinuation of the other anticataplectic and stabilized during SDP. In cataplexy treatment-naïve participants, cataplexy decreased consistently from week one of JZP-258 titration through the end of SDP.

At the end of the double-blind withdrawal period, there was a significant increase in median ESS scores in participants randomized to placebo compared with participants randomized to JZP-258 (median [Q1, Q3]: 2.0 [0.0, 5.0] vs 0.0 [-1.0, 1.0], respectively; treatment difference, $P < 0.0001$). Additionally, both patient and clinician ratings of change in narcolepsy symptoms overall (PGIc and CGIc) indicated worsening in more participants randomized to placebo compared with participants randomized to JZP-258 ('Much Worse' or 'Very Much Worse' scores for placebo vs JZP-258: PGIc, 44.6% vs 4.3%; CGIc, 60.0% vs 5.9%; $P < 0.0001$ [nominal]).

"It's encouraging to see these positive results from the Phase 3 study, as JZP-258 may represent an important and novel product candidate for people with narcolepsy with the benefit of a 92% reduction in sodium compared to sodium oxybate," said Richard K. Bogan, MD, FCCP, FAASM, associate clinical professor at the University of South Carolina School of Medicine, chief medical officer at SleepMed in Columbia, SC and lead investigator of this study. "This is important for people living with narcolepsy because narcolepsy is a chronic condition that may require lifelong treatment, and is associated with increased risk of comorbid conditions, including hypertension and cardiovascular disease."

The overall safety profile in the Phase 3 study of JZP-258 was consistent with that reported in clinical trials of sodium oxybate. The most common adverse events reported by $\geq 5\%$ of participants while taking JZP-258 in the Phase 3 study were headache, nausea and dizziness. Two participants experienced serious adverse events that were considered by the investigator to be treatment-related (confusional state and visual hallucination after accidental JZP-258 overdose; muscle enzymes increased one day after the end of placebo treatment).

About Narcolepsy

Narcolepsy is a chronic, debilitating neurological disorder characterized by excessive daytime sleepiness, and the inability to regulate sleep-wake cycles normally.¹ It affects an estimated one in 2,000 people in the United States, with symptoms typically appearing in childhood. It is estimated that more than 50% of people with narcolepsy have not been diagnosed.² Studies have shown it may take 10 years or more for people with narcolepsy to receive a diagnosis.³ Excessive daytime sleepiness is the primary symptom of narcolepsy and is present in all people with the disorder.⁴ Excessive daytime sleepiness is characterized by the inability to stay awake and alert during the day resulting in drowsiness and unplanned lapses into sleep.^{2,4,5} There are five primary symptoms of narcolepsy, including excessive daytime sleepiness, cataplexy, disrupted nighttime sleep, sleep-related hallucinations, and sleep paralysis.⁶ While all people with narcolepsy experience excessive daytime sleepiness, not all individuals with narcolepsy experience all five symptoms.^{7,8}

About Cataplexy

Cataplexy, the most specific symptom of narcolepsy, is the sudden, generally brief (<2 minutes) loss of muscle tone with retained consciousness. It is usually triggered by strong emotions, such as laughter, surprise, or anger.^{7,8,9} Although many emotions can potentially lead to cataplexy, those associated with mirth are usually the most potent.⁷ Cataplexy occurs in about 70% of people with narcolepsy.¹⁰ Presentation differs widely among people with narcolepsy, ranging from sporadic partial attacks triggered by laughter to frequent complete collapse brought about by a variety of emotions.^{6,7} Complete collapse is less common.⁸ More commonly, episodes of cataplexy involve only certain muscle groups, such as arms and legs (e.g., knees buckling), the head and neck (e.g., head drooping), or the face and jaw (e.g., sagging, slurred speech, eyelid drooping).^{7,8,9,10}

About JZP-258

JZP-258 is an investigational product being evaluated in adults for the treatment of cataplexy and excessive daytime sleepiness in narcolepsy, as well as for the treatment of idiopathic hypersomnia. JZP-258 is a novel oxybate product candidate with a unique composition of cations resulting in 92% less sodium than Xyrem[®] (sodium oxybate). While the exact mechanism of action of JZP-258 is not fully understood, it is hypothesized that the therapeutic effects of JZP-258 on sleep/wake symptoms are mediated through modulation of GABA_B during sleep.

About Jazz Pharmaceuticals plc

Jazz Pharmaceuticals plc (Nasdaq: JAZZ), a global biopharmaceutical company, is dedicated to developing life-changing medicines for people with limited or no options. As a leader in sleep medicine and with a growing hematology/oncology portfolio, Jazz has a diverse portfolio of products and product candidates in development, and is focused on transforming biopharmaceutical discoveries into novel medicines. Jazz Pharmaceuticals markets Sunosi[™] (solriamfetol), Xyrem[®] (sodium oxybate) oral solution, Defitelio[®] (defibrotide sodium), Erwinaze[®] (asparaginase Erwinia chrysanthemi) and Vyxeos[®] (daunorubicin and cytarabine) liposome for injection in the U.S. and markets Defitelio[®] (defibrotide), Erwinase[®] and Vyxeos[®] 44 mg/100 mg powder for concentrate for solution for infusion in countries outside the U.S. For country-specific product information, please visit www.jazzpharmaceuticals.com/medicines. For more information, please visit www.jazzpharmaceuticals.com and follow us on Twitter at [@JazzPharma](https://twitter.com/JazzPharma).

"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 company's belief that JZP-258, if approved, will provide a clinically meaningful benefit to patients prescribed oxybate and an important and novel product candidate for people with narcolepsy, and other statements that are not historical facts. These forward-looking statements are based on the company's 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: the uncertain regulatory approval process, including the risk that the company's planned JZP-258 new drug application may not be submitted, accepted or approved by the FDA in a timely manner or at all; effectively commercializing JZP-258, if approved; 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 the company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2019 and future filings and reports by the company. Other risks and uncertainties of which the company is not currently aware may also affect the company's 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 the company on its website or otherwise. The company 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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