Jazz Pharmaceuticals Announces Positive Results from the Phase 3 TONES 3 and TONES 4 Studies of JZP-110 in Patients with Obstructive Sleep Apnea

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Abstracts Accepted for Presentation at the 31st Annual Meeting of the Associated Professional Sleep Societies LLC (APSS) in June 2017

DUBLIN, March 20, 2017 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced positive efficacy results from two global multicenter studies in adult patients with excessive sleepiness associated with obstructive sleep apnea (OSA). JZP-110 demonstrated highly statistically significant differences in the co-primary efficacy endpoints in the TONES 3 study at the 300 mg, 150 mg, 75 mg and 37.5 mg dose arms and in the TONES 4 study in the combined JZP-110 treatment arm (300 mg, 150 mg, and 75 mg doses) compared to placebo. Based on the preliminary safety analysis, the most commonly reported adverse events (AEs) in these studies were consistent with those previously described in the Phase 2 clinical studies evaluating JZP-110 in narcolepsy.

"There is an important unmet need for OSA patients who experience excessive sleepiness, and the robust magnitude of effect, when taken together with the preliminary safety findings, suggest that JZP-110 could be an important treatment option for this population," said Karen Smith, M.D., Ph.D., global head of research and development and chief medical officer of Jazz Pharmaceuticals. "We are grateful to the patients and the investigators who participated in these studies and look forward to presenting the results from the Phase 3 OSA studies at the APSS meeting in June. We expect to announce preliminary results from our Phase 3 TONES 2 study evaluating JZP-110 in excessive sleepiness associated with narcolepsy in the second quarter of 2017. Subject to final data analysis and regulatory discussions with FDA, we continue to target NDA submission in late 2017."

"Independent of CPAP therapy for OSA, there can be a level of excessive sleepiness associated with reduced quality of life and 'fall asleep' accidents, with increased public risks of drowsy driving," said Kingman Strohl, M.D., Professor of Medicine, University Hospitals Case Medical Center and Case School of Medicine, Cleveland OH. "Given this, clinical recognition and meaningful treatment options are needed for OSA patients who experience excessive sleepiness."

The Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) Phase 3 program is comprised of four studies, two in OSA, one in narcolepsy and one open-label, long-term safety and maintenance of efficacy study. The two Phase 3 OSA studies enrolled 652 total patients.

Efficacy Results of TONES 3 Study

The TONES 3 study, or 14-003, is a 5-arm, parallel-group study evaluating four doses of JZP-110 (300 mg, 150 mg, 75 mg and 37.5 mg) and placebo for a 12-week period. The study enrolled 476 patients and was powered to detect differences between placebo and the 300 mg and 150 mg dose arms.

In TONES 3, JZP-110 demonstrated highly statistically significant improvement in the co-primary endpoints of Maintenance of Wakefulness test (MWT) and Epworth Sleepiness scale (ESS) at all doses. In addition, the key secondary endpoint of Patient Global Impression of Change (PGIc) scale demonstrated a highly statistically significant improvement in the 300 mg, 150 mg and 75 mg doses versus placebo. On the co-primary endpoints of MWT and ESS, the study demonstrated that treatment with JZP-110 significantly increased the patients' ability to stay awake and significantly decreased patients' subjective levels of sleepiness, respectively, compared to placebo. These effects were maintained throughout the course of the study.

Efficacy Results of TONES 4 Study

The TONES 4 study, or 14-004, is a six-week study in which eligible subjects received four weeks of open-label treatment, and at the end of week 4, 126 patients who reported "much" or "very much" improvement on the PGIc scale and who had numerical improvements on the MWT and ESS at week 4 were then randomized 1:1 to receive either the same dose of JZP-110 received in the stable dose phase, or placebo, for two weeks in the randomized withdrawal phase.

In TONES 4, patients randomized to continue on JZP-110 maintained efficacy, while those randomized to placebo experienced a loss of efficacy, as measured by the co-primary and key secondary endpoints.

Preliminary Safety Results of TONES 3 and TONES 4 Studies

Based on a preliminary safety analysis, the most commonly reported adverse events were headache, nausea, decreased appetite, dry mouth, anxiety, dizziness, insomnia, nasopharyngitis, and palpitations. There were six patients with serious adverse events (SAEs), two patients on placebo and four on JZP-110. None of these was deemed a treatment-related adverse event as assessed by the investigators. Additional safety information will be available based on the final analyses of the JZP-110 program, including results of the open-label, long-term safety and maintenance of efficacy study.

About the TONES 3 and TONES 4 Studies

TONES 3 is a 12-week, 5-arm, parallel-group, double-blind, placebo-controlled, randomized Phase 3 study, evaluating the safety and efficacy of JZP-110 at 300 mg, 150 mg, 75 mg and 37.5 mg compared to placebo. The co-primary endpoints are the change in mean sleep latency on the MWT and the change in the ESS score, from baseline to week 12. The key secondary endpoint is the change on the PGIc scale, a patient-reported measure of improvement, worsening, or no change in overall condition from baseline to week 12.

TONES 4 is a six-week Phase 3 study comprising a two-week flexible-dose titration phase followed by two weeks at stable dose, and then a two-week, placebo-controlled, double-blind randomized withdrawal phase. In this study, patients were first titrated to a maximum tolerated dose over a two-week period and then continued on that dose for two weeks in a stable dose phase. The primary analyses evaluated the difference between JZP-110 treatment versus placebo on the co-primary endpoints of MWT and ESS, measured from the end of the stable dose phase at week 4 to the end of the randomized withdrawal phase at week 6.

About OSA and Excessive Sleepiness

OSA is a highly prevalent disease with excessive sleepiness reported as one of the most frequent symptoms. Excessive sleepiness is associated with impairments in function, vigilance, concentration, thinking, social interactions and quality of life. Positive airway pressure (PAP) therapy, commonly referred to as continuous positive airway pressure (CPAP), has been shown to be an effective therapy for sleep-related airway obstruction, with frequent improvement in excessive sleepiness in many patients; however, approximately 25-50% of patients with OSA experience difficulty with PAP therapy. In addition, many patients treated with PAP therapy continue to experience persistent sleepiness, despite successful use of PAP.

About JZP-110

JZP-110 is a selective dopamine and norepinephrine reuptake inhibitor (DNRI) in late-stage development for treatment of excessive sleepiness in adult patients with narcolepsy or OSA. Jazz Pharmaceuticals has worldwide development, manufacturing, and commercialization rights to JZP-110, excluding certain jurisdictions in Asia. JZP-110 has orphan drug designation in the United States for narcolepsy. Across the entire JZP-110 development program, over 2,000 subjects have enrolled in 20 studies. The JZP-110 Phase 3 clinical program includes two studies evaluating excessive sleepiness in adult patients with OSA, one study evaluating excessive sleepiness in adult patients with narcolepsy and an open-label, long-term safety and maintenance of efficacy study. Enrollment is complete in all studies that are expected to support the planned JZP-110 New Drug Application (NDA) submission to the U.S. Food and Drug Administration (FDA).

About Jazz Pharmaceuticals

Jazz Pharmaceuticals plc (Nasdaq: JAZZ) is an international biopharmaceutical company focused on improving patients' lives by identifying, developing and commercializing meaningful products that address unmet medical needs. The company has a diverse portfolio of products and product candidates, with a focus in the areas of sleep and hematology/oncology. In these areas, Jazz Pharmaceuticals markets Xyrem® (sodium oxybate) oral solution, Erwinaze® (asparaginase *Erwinia chrysanthemi*) and Defitelio® (defibrotide sodium) in the U.S. and markets Erwinase® and Defitelio® (defibrotide) in countries outside the U.S. For more information, please visit www.jazzpharmaceuticals.com.

"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 JZP-110 as a potential treatment for excessive sleepiness in adult patients with OSA, the expected announcement of preliminary results from the company's Phase 3 TONES 2 study evaluating JZP-110 in excessive sleepiness associated with narcolepsy, the company's plans for submission of an NDA for JZP-110 with the FDA, the timing of such events and activities, 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: pharmaceutical product development and clinical success thereof, the regulatory approval process, including the risk that the company may be unable to obtain approval by the FDA for JZP-110, and effectively commercializing JZP-110, 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 Annual Report on Form 10-K for the period ended December 31, 2016 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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