Jazz Pharmaceuticals Presents JZP-110 Data in Patients with Excessive Sleepiness Associated with Obstructive Sleep Apnea

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Data were presented in a poster presentation at the annual SLEEP Meeting; JZP-110 U.S. NDA submission planned for later this year

DUBLIN, June 6, 2017 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today presented positive efficacy results from its global multicenter studies (TONES 3 and TONES 4) of JZP-110 in adult patients with excessive sleepiness associated with obstructive sleep apnea (OSA). The data were presented in a poster session at the 31st Associated Professional Sleep Societies (APSS) Annual SLEEP Meeting in Boston.

"Obstructive sleep apnea (OSA) is a serious chronic sleep disorder in which breathing repeatedly stops and starts during sleep," said Karen Smith, M.D., Ph.D., executive vice president of research and development and chief medical officer of Jazz Pharmaceuticals. "These studies suggest that JZP-110 could provide an important treatment option for patients with excessive sleepiness with OSA who may not respond to, or may experience inadequate response to, their current wake-promoting therapies. It also underscores our commitment to making significant research and development investments to find innovative treatments for unmet medical needs in sleep medicine."

"People who experience excessive sleepiness associated with OSA may have an inadequate response to attempts to treat the OSA, underscoring the need for new treatment options for residual sleepiness that may affect their quality of life," said Kingman Strohl, M.D., Professor of Medicine, University Hospitals Case Medical Center and Case School of Medicine, Cleveland OH. "The results with JZP-110 show significant increase in a patients' ability to stay awake and decreased patients' subjective levels of sleepiness compared to placebo, in a rather customary practice setting."

The Treatment of OSA and Narcolepsy Excessive Sleepiness (TONES) Phase 3 program is comprised of four studies, one study evaluating excessive sleepiness in adult patients with narcolepsy (TONES 2), two studies evaluating excessive sleepiness in adult patients with OSA (TONES 3 and TONES 4), and an open-label, long-term safety and maintenance of efficacy study (TONES 5) in the treatment of excessive sleepiness in patients with narcolepsy or OSA.

About the Global Phase 3 TONES 3 Study

TONES 3 was a 12-week, 5-arm, parallel-group, double-blind, placebo-controlled, randomized Phase 3 study that evaluated the safety and efficacy of JZP-110 at 300 mg, 150 mg, 75 mg, and 37.5 mg compared to placebo, in adults with excessive sleepiness in OSA. Patients (N=476) were randomized 1:1:2:2:2 to JZP-110 37.5 mg (n=59), 75 mg (n=61), 150 mg (n=118), 300 mg (n=119), or placebo (n=119). The co-primary endpoints were the change in mean sleep latency on the Maintenance of Wakefulness Test (MWT) and in the Epworth Sleepiness Scale (ESS) score, from baseline to week 12. The key secondary endpoint was the percentage of patients who reported improvement on the Patient Global Impression of Change (PGIc) scale, a patient-reported measure of overall condition from baseline to week 12.

In adult patients with OSA, JZP-110 at all doses demonstrated statistically significant improvements on the co-primary endpoints of mean sleep latency on the MWT and the ESS from baseline to week 12 compared to placebo. The endpoints of MWT and ESS measure patients' ability to stay awake and patients' subjective levels of sleepiness, respectively. JZP-110 increased the mean MWT sleep latency by more than 10 minutes at all time points at the 150 and 300 mg doses. JZP-110 decreased mean ESS scores by more than 7 points at the 150 and 300 mg doses at week 12.

On the key secondary endpoint of the PGIc scale, patients reported significant overall improvement compared to placebo at week 12 on all doses of JZP-110 except for 37.5 mg. Approximately 90% of patients reported overall improvement on the 150 and 300 mg doses at week 12.

Results from the primary analysis of the co-primary endpoints of MWT and ESS, and analysis of the key secondary endpoint of PGIc were:

	Change (SE) from Baseline to Week 12				
TONES 3 Study Results (mITT population, N=459)	**JZP-110 300 mg** (N=115)	**JZP-110 150 mg** (N=116)	**JZP-110 75 mg** (N=58)	**JZP-110 37.5 mg** (N=56)	**Placebo** (N=114)
Mean Sleep Latency on Maintenance of Wakefulness Test (MWT): Increased ability to stay awake	13.0 min (1.0) *p<0.0001*	11.0 min (1.0) *p<0.0001*	9.1 min (1.4) *p<0.0001*	4.7 min (1.4) p<0.05	0.2 min (1.0)
Epworth Sleepiness Scale (ESS): Decreased subjective sleepiness	-7.9 (0.5) *p<0.0001*	-7.7 (0.4) *p<0.0001*	-5.0 (0.6) *p<0.05*	-5.1 (0.6) *p<0.05*	-3.3 (0.5)
Patient Global Impression-Change (PGIc): Minimal, much, or very much improvement	88.7% *p<0.0001*	89.7% *p<0.0001*	72.4% *p<0.05*	55.4% *p=0.4447*	49.1%

Of the 476 randomized subjects, 404 completed the 12-week treatment. Twenty-nine patients (6.1%) in the safety population: four patients (3.4%) on placebo and 25 (7.0%) on JZP-110, discontinued due to treatment emergent adverse events (TEAEs). The most commonly reported TEAEs (occurring in ≥5% of patients across all doses of JZP-110) in the TONES 3 study were headache, nausea, decreased appetite, anxiety, and nasopharyngitis. There were seven serious TEAEs reported in five patients: goiter (n=1), and a motor vehicle accident, back pain, and sciatica (n=1)

in two patients on placebo; bile duct obstruction (n=1) and streptococcal endocarditis (n=1) in two patients on JZP-110 37.5 mg; and hyperglycemia (n=1) in one patient on JZP-110 150 mg. One subject had a non-treatment emergent SAE of coronary artery disease that started prior to receiving JZP-110 300 mg and that was not reported until after dosing. TEAEs and discontinuations due to an AE were most common at the JZP-110 300 mg dose.

About the Global Phase 3 TONES 4 Study

TONES 4 was a six-week Phase 3 study comprising a two-week flexible-dose titration phase followed by two-weeks of stable dose treatment. Patients who reported 'much' or 'very much' improvement and who had numerical improvements on the MWT and ESS at the end of the stable dose phase (week 4) then entered a two-week, placebo-controlled, double-blind randomized withdrawal phase. In this study, 174 patients were titrated to a maximum tolerated dose over a two-week period, and 157 patients continued on that dose for two weeks in the stable dose phase. The primary analysis (n=122 in the modified intent to treat (mITT) population) 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.

Patients who completed the 4-week treatment and remained on JZP-110 did not demonstrate loss of efficacy relative to those who were randomized to placebo.

Results from the primary analysis of the co-primary endpoints of MWT and ESS, and analysis of the key secondary endpoint of PGIc were:

	Change (SE) from Week 4 to Week 6	
TONES 4 Study Results (mITT population)	**JZP-110** (N=60)	**Placebo** (N=62)
Mean Sleep Latency on Maintenance of Wakefulness Test (MWT): Ability to stay awake	-1.0 min (1.4) *p<0.0001*	-12.1 min (1.3)
Epworth Sleepiness Scale (ESS): Subjective sleepiness	-0.1 (0.7) *p<0.0001*	4.5 (0.7)
Patient Global Impression-Change (PGIc): Minimally, much, or very much worse	20.0% *p<0.0001*	50.0%

During the double-blind withdrawal phase (weeks 4 to 6), patients who continued on JZP-110 remained improved on the MWT and ESS. Patients who switched to placebo showed worsening of sleepiness, with mean MWT sleep latency decreased by 12.1 minutes from week 4 to week 6 (compared with a decrease of 1.0 minute for those who remained on JZP-110, p<0.0001) and mean ESS scores increased by 4.5 minutes (compared to a mean decrease of 0.1 minutes for those who stayed on JZP-110, p<0.0001).

A significantly higher percentage of patients who were switched to placebo experienced a worsening of their overall condition on the PGIc as compared with patients who stayed on JZP-110 (p<0.0001).

There were no serious TEAEs. Six patients (3.4%) withdrew from the study due to TEAEs. Most TEAEs occurred during the titration phase of the study. The most common TEAEs (occurring in ≥5% patients) during the titration phase were headache, dry mouth, nausea, dizziness, and insomnia.

Full details of the APSS annual SLEEP meeting can be found at http://www.sleepmeeting.org/.

About OSA and Excessive Sleepiness

OSA is a highly prevalent disease (as high as 24% in men and 9% in women[1]) 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 development for treatment of excessive sleepiness in adult patients with narcolepsy, OSA, and Parkinson's disease. In 2014, Jazz Pharmaceuticals acquired a license to develop and commercialize JZP-110 from SK Biopharmaceuticals, which discovered the compound. Jazz Pharmaceuticals has worldwide development, manufacturing, and commercialization rights to JZP-110, excluding certain jurisdictions in Asia. SK Biopharmaceuticals maintains rights in Korea, Japan, China, Taiwan, Singapore, Indonesia, India, Philippines, Thailand, Malaysia, Vietnam, and Hong Kong. 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 one study evaluating excessive sleepiness in adult patients with narcolepsy (TONES 2), two studies evaluating excessive sleepiness in adult patients with OSA (TONES 3 and TONES 4), and an open-label, long-term safety and maintenance of efficacy study (TONES 5) in the treatment of excessive sleepiness in patients with narcolepsy or OSA. Enrollment is complete in all studies that are expected to support Jazz Pharmaceuticals' planned JZP-110 New Drug Application (NDA) submission to the U.S. Food and Drug Administration (FDA) in late 2017.

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 company's commitment to making significant research and development investments to find innovative treatments for unmet medical needs in sleep medicine, the company's plans for submission of an NDA for JZP-110 with the FDA and the timing thereof, 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 in a timely manner or at all; 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 Quarterly Report on Form 10-Q for the quarter ended March 31, 2017 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.

Reference:

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. Apr 29 1993;328(17):1230-1235

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