Avadel Pharmaceuticals Announces Journal of Urology Publication of Phase 3 Data on NOCTIVA

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NOCTIVA is the first treatment approved by the FDA to treat nocturia in adults due to nocturnal polyuria

DUBLIN, Ireland, Sept. 28, 2018 (GLOBE NEWSWIRE) -- Avadel Pharmaceuticals plc (Nasdaq: AVDL), a company focused on providing innovative medicines for chronic urological, central nervous system, and sleep disorders, announced today that the *Journal of Urology*, official journal of the American Urological Association, recently published results from pivotal Phase 3 clinical trial data on NOCTIVA™ (desmopressin acetate) Nasal Spray, the lowest effective dose of desmopressin. These data showed that treatment with NOCTIVA resulted in significant reductions in nocturic episodes in patients with nocturia. Additionally, NOCTIVA showed improvements in patients' quality of life (QoL) and had a well-tolerated safety profile. These results demonstrate that NOCTIVA is an effective treatment for adults with nocturia due to nocturnal polyuria.

"We are extremely pleased that these pivotal results on NOCTIVA were published in the well-respected *Journal of Urology*," said Greg Divis, Chief Operating Officer of Avadel Pharmaceuticals. "We understand how disruptive nocturia can be for patients and are proud to have recently launched NOCTIVA, the first product approved by the FDA for nocturia due to nocturnal polyuria."

Noctiva is a proprietary emulsified formulation of desmopressin that uses a unique permeation enhancer to deliver a microdose of desmopressin. It is the lowest effective dose of desmopressin approved by the FDA to treat nocturia in adults due to nocturnal polyuria, which causes patients to wake two or more times per night to urinate. Nocturia affects an estimated 50 million Americans[1] and can have an adverse impact on QoL and overall health with an increased risk of diabetes, hypertension, depression, injury due to falls, and decreased daytime functioning and work productivity.[2]

In two double-blind, placebo controlled, Phase 3 trials, DB3 and DB4, 1,333 patients with a mean of 2.16 or more nocturic voids (NOV) per night were randomized to NOCTIVA 1.66 or 0.83 mcg, or placebo, for a 12-week treatment period. Existing etiologies of nocturia included nocturnal polyuria (80 percent), benign prostatic hyperplasia (39 percent), and overactive bladder (27 percent). Co-primary end points were the mean reduction in nocturic episodes per night from baseline and the percent of patients with a 50 percent or greater reduction in mean nocturic episodes per night. Secondary end points were the validated INTU (Impact of Nighttime Urination) questionnaire (in DB4 only), time to first nocturic void, the percent of nights with one or fewer nocturic voids and the reduction in volume of urine produced at night.

The results showed that reduction in mean nocturic episodes per night from baseline were significantly greater with NOCTIVA 0.83 mcg and 1.66 mcg compared to placebo in both DB3 (-1.4 and -1.6 respectively, vs -1.2, placebo) and DB4 (-1.4 and -1.5 respectively, vs -1.2 placebo). The percentage of patients who achieved a 50 percent reduction in mean nocturic episodes per night was significantly higher with the NOCTIVA 1.66 mcg dose compared with placebo in the DB3 (52 percent vs 32.8 percent) and DB4 (46.5 percent vs 28.5 percent) studies, as well as the pooled analysis of both studies (48.7 percent vs 30.3 percent). A significant difference was also observed with the 0.83 mcg dose compared with placebo in the pooled analysis (37.9 percent vs 30.3 percent).

Both doses of NOCTIVA had an acceptable safety profile and were well tolerated. The most common adverse events of nasal discomfort and nasopharyngitis were mild to moderate in intensity and occurred with similar incidence in the placebo group. Incidence of hyponatremia, defined as serum sodium ≤125 mmol/L regardless of symptoms or <130 mmol/L with symptoms, was low and occurred in five patients (1.1 percent) at the higher dose and in one patient (0.2 percent) who received placebo. No patient receiving the 0.83 mcg dose developed hyponatremia.

In secondary endpoints, patients receiving the 1.66 mcg dose had a statistically significant improvement in the overall impact score reported on the INTU ($p = 0.0225$) indicating better quality of life and a clinically meaningful benefit. These results mark the first time a decrease in nocturic episodes was correlated with improvement in patients' quality of life in terms of how they feel and function. Compared with placebo in DB3 and DB4 studies and in the pooled analysis, both strengths of NOCTIVA significantly increased the time from bedtime to the first nocturic void. There was also a significant increase in the percent of nights with one or fewer nocturic episodes after treatment with NOCTIVA 1.66 mcg dose compared with placebo; in the pooled analysis both 0.83 mcg and 1.66 mcg doses showed significant improvement compared to placebo.

"We are very pleased that NOCTIVA 1.66 mcg met all co-primary and secondary endpoints in these trials," said Jed Kaminetsky, Clinical Assistant Professor, Department of Urology, NYU Langone Health and Medical Director Manhattan Medical Research. "Nocturia is not only highly bothersome but has an impact on patients' quality of life and overall health. Having a safe, effective medication to treat my patients suffering from nocturia due to nocturnal polyuria is a game changer for their quality of life."

About Nocturia

Nocturia is a highly prevalent, under-recognized condition associated with disrupted sleep, which results in reduced productivity and negatively impacts health and quality of life. [3],[4],[5],[6],[7],[8],[9]

About NOCTIVA

NOCTIVA is an emulsified microdose vasopressin analog, approved by the FDA for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least two times per night to void. It is administered through a preservative-free intranasal delivery system as a single spray in one nostril approximately 30 minutes before bedtime. NOCTIVA is approved in two dosage forms of 0.83 mcg and 1.66 mcg. For more information, please visit www.noctiva.com.

WARNING: HYPONATREMIA

See full prescribing information for complete boxed warning.

Important Safety Information for NOCTIVA (desmopressin acetate)
WARNING: HYPONATREMIA

- **NOCTIVA can cause hyponatremia, which may be life-threatening if severe.**
- **NOCTIVA is contraindicated in patients at increased risk of severe hyponatremia, such as patients with excessive fluid intake, illnesses that can cause fluid or electrolyte imbalances, and in those using loop diuretics or systemic or inhaled glucocorticoids.**
- **Ensure serum sodium is normal before starting or resuming NOCTIVA. Measure serum sodium within seven days and approximately one month after initiating therapy or increasing the dose, and periodically during treatment. More frequently monitor serum sodium in patients 65 years of age and older and in patients at increased risk of hyponatremia.**
- **If hyponatremia occurs, NOCTIVA may need to be temporarily or permanently discontinued.**

INDICATIONS AND USAGE
NOCTIVA is a vasopressin analog indicated for the treatment of nocturia due to nocturnal polyuria in adults who awaken at least 2 times per night to void.

Limitation of Use: Not studied in patients younger than 50 years of age.

CONTRAINDICATIONS

- Hyponatremia or a history of hyponatremia
- Polydipsia
- Primary nocturnal enuresis
- Concomitant use with loop diuretics or systemic or inhaled glucocorticoids
- Estimated glomerular filtration rate below 50 mL/min/1.73 m^2
- Syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- During illnesses that can cause fluid or electrolyte imbalance
- New York Heart Association (NYHA) Class II-IV congestive heart failure
- Uncontrolled hypertension

WARNINGS AND PRECAUTIONS

- Fluid retention: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention. Monitor volume status in patients with NYHA Class I congestive heart failure.
- Nasal conditions: Discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved.

ADVERSE REACTIONS
Common adverse reactions in clinical trials (incidence >2%) included nasal discomfort, nasopharyngitis, nasal congestion, sneezing, hypertension / blood pressure increased, back pain, epistaxis, bronchitis and dizziness.

DRUG INTERACTIONS
Monitor serum sodium more frequently when NOCTIVA is concomitantly used with drugs that may cause water retention and increase the risk for hyponatremia (e.g., tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, nonsteroidal anti-inflammatories, lamotrigine and carbamazepine).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use of NOCTIVA is not recommended.
- Pediatric: Do not use NOCTIVA for primary nocturnal enuresis in children.

To report SUSPECTED ADVERSE REACTIONS, contact Avadel at 1-877-638-4579 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the full Prescribing Information for NOCTIVA™ at www.Noctiva.com/prescribing-information.

About Avadel Pharmaceuticals
Avadel Pharmaceuticals plc (Nasdaq:AVDL) is a specialty pharmaceutical company that seeks to develop differentiated pharmaceutical products that are safe, effective and easy to take through formulation development, by utilizing its proprietary drug delivery technology and through in-licensing / acquiring new products; ultimately, helping patients adhere to their prescribed medical treatment and see better results. Avadel's current portfolio of products and product candidates focuses on the urology, central nervous system (CNS) / sleep, and hospital markets. The Company is headquartered in Dublin, Ireland with operations in St. Louis, Missouri and Lyon, France. For more information, please visit www.avadel.com.

Safe Harbor: *This press release may include forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. The words "will," "may," "believe," "expect," "anticipate," "estimate," "project" and similar expressions, and the negatives thereof, identify forward-looking statements, each of which speaks only as of the date the statement is made. Although we believe that our forward-looking statements are based on reasonable assumptions within the bounds of our knowledge of our business and operations, our business is subject to significant risks and as a result there can be no assurance that actual results of our research, development and*

commercialization activities and our results of operations will not differ materially from the results contemplated in such forward-looking statements. These risks include: (i) risks relating to our exchangeable senior notes including use of the net proceeds from the offering of the notes and other future events related to the notes; (ii) risks relating to the divestiture of our former pediatric business including whether such divestiture will be accretive to our operating income and cash flow; (iii) risks relating to our license agreement with Serenity Pharmaceuticals, LLC including that a potential competitive product, and patent litigation with the manufacturer of that product, could have a material adverse impact on our ability to successfully exploit any market opportunity for the drug desmopressin acetate (the "Drug") which we are marketing under the brand name Noctiva [tm], our internal analyses may overstate the market opportunity in the United States for the Drug or we may not effectively exploit such market opportunity, that significant safety or drug interaction problems could arise with respect to the Drug, that we may not successfully increase awareness of nocturia and the potential benefits of the Drug, and that the need for management to focus attention on the development and commercialization of the Drug could cause our ongoing business operations to suffer; and (iv) the other risks, uncertainties and contingencies described in the Company's filings with the U.S. Securities and Exchange Commission, including our annual report on Form 10-K for the year ended December 31, 2017, in particular disclosures that may be set forth in particular under the captions "Forward-Looking Statements" and "Risk Factors," including without limitation: our dependence on a small number of products and customers for the majority of our revenues; the possibility that our Bloxiverz®,Vazculep® and Akovaz® products, which are not patent protected, could face substantial competition resulting in a loss of market share or forcing us to reduce the prices we charge for those products; the possibility that we could fail to successfully complete the research and development for pipeline products we are evaluating for potential application to the FDA pursuant to our "unapproved-to-approved" strategy, or that competitors could complete the development of such products and apply for FDA approval of such products before us; the possibility that our products may not reach the commercial market or gain market acceptance; our need to invest substantial sums in research and development in order to remain competitive; our dependence on certain single providers for development of several of our drug delivery platforms and products; our dependence on a limited number of suppliers to manufacture our products and to deliver certain raw materials used in our products; the possibility that our competitors may develop and market technologies or products that are more effective or safer than ours, or obtain regulatory approval and market such technologies or products before we do; the challenges in protecting the intellectual property underlying our drug delivery platforms and other products; and our dependence on key personnel to execute our business plan.

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