Avadel Pharmaceuticals Announces Publication of Positive Secondary Endpoint Data from Pivotal Phase 3 REST-ON Trial

April 6, 2022

- *Once-at-bedtime FT218 demonstrated clinically meaningful improvement in assessments of disrupted nighttime sleep compared to placebo in adults with narcolepsy*
- *New data bolster positive primary endpoint data from the completed Phase 3 REST-ON trial and indicate that FT218 positively impacts both daytime and nighttime symptoms of narcolepsy*

DUBLIN, Ireland, April 06, 2022 (GLOBE NEWSWIRE) -- Avadel Pharmaceuticals plc (Nasdaq: AVDL), a biopharmaceutical company focused on transforming medicines to transform lives, announced today the publication of positive secondary endpoint data from its pivotal Phase 3 REST-ON trial of FT218 in *CNS Drugs*, a peer-reviewed medical journal focused on the treatment of psychiatric and neurological disorders. The paper, titled "Effect of FT218, a Once-Nightly Sodium Oxybate Formulation, on Disrupted Nighttime Sleep in Patients With Narcolepsy: Results From the Randomized Phase 3 REST-ON Trial," can be accessed at https://link.springer.com/article/10.1007/s40263-022-00904-6. FT218, also referred to in Avadel's scientific publications as ON-SXB, is the Company's lead drug candidate, an investigational formulation of sodium oxybate designed to be taken once at bedtime for the treatment of excessive daytime sleepiness (EDS) or cataplexy in adults with narcolepsy.

Approximately 65% of people with narcolepsy are estimated to have nocturnal sleep disturbances.[1] While people living with narcolepsy may be able to fall asleep easily, their sleep tends to include frequent arousals and stage shifts and is often not refreshing. Most treatments for narcolepsy are taken in the morning to combat EDS; only oxybate treatments are taken at bedtime, with current immediate-release formulations taken twice nightly. To evaluate the potential for improvement on sleep architecture with a single bedtime dose of FT218, secondary endpoints from the double-blind, placebo-controlled REST-ON trial were assessed, including polysomnographic measures of sleep stage shifts and nocturnal arousals. In addition, patient-reported assessments of sleep quality and refreshing nature of sleep, as measured on a visual analog scale, were analyzed. Highlights from the analyses follow:

- At all doses evaluated (6, 7.5 and 9 g), once-at-bedtime FT218 demonstrated a statistically significant decrease in the number of transitions from stages N1, N2, N3, and rapid eye movement (REM) sleep to wake and from N2, N3, and REM sleep to N1 ($P<0.001$ at all doses) and number of nocturnal arousals ($P<0.05$ at 6 g; $P<0.001$ at 7.5 and 9 g) compared to placebo.
- Sleep quality and refreshing nature of sleep were significantly improved with all evaluated doses compared to placebo ($P<0.001$).
- A post-hoc analysis showed that significant improvements in DNS were observed regardless of concomitant stimulant use.
- Additional post-hoc data further supported improvements in sleep architecture with increases in N3, or slow wave sleep and increased REM latency.

"DNS is a frequent, bothersome, but often minimized symptom of narcolepsy," said Thomas Roth, Ph.D., lead author and Director of the Sleep Disorders and Research Center at Henry Ford Hospital. "These data show that FT218 improved both objective and subjective assessments of DNS, as measured by polysomnographic recordings and the participants' own assessments. These results will be relevant for the sleep medicine community to consider in treatment selection, if FT218 is approved."

The primary safety and efficacy results from REST-ON were published in August 2020 in *SLEEP* by Kushida et al. The most common adverse events (incidence > 5% and greater than placebo) in patients receiving FT218 were nausea, dizziness, enuresis, headache and vomiting. Additional secondary and post-hoc data were presented at SLEEP (the annual Meeting of the Associated Professional Sleep Societies) and World Sleep.

"While the treatment of narcolepsy often focuses on alleviating daytime symptoms, such as EDS, these results highlight the importance of a potential treatment option that also addresses nighttime symptoms," said Douglas Williamson, M.D., Chief Medical Officer of Avadel. "This peer-reviewed publication marks the first time that improvements in sleep quality, refreshing nature of sleep and DNS have been demonstrated with an oxybate in one uninterrupted, consolidated sleep segment. The full body of evidence for once-at-bedtime FT218, including previously published results demonstrating its positive impact on EDS and cataplexy, reinforce our confidence in its potential, if approved, as a major advance for the treatment of narcolepsy."

About Narcolepsy
Narcolepsy is a chronic neurological condition that impairs the brain's ability to regulate the sleep-wake cycle. The condition affects approximately one in 2,000 people in the United States with the cardinal symptom of EDS. Additional symptoms can vary by person and may include DNS, a sudden loss of muscle tone usually triggered by strong emotion (cataplexy), sleep paralysis and hypnagogic hallucinations.

About FT218
FT218 is an investigational formulation of sodium oxybate leveraging our proprietary drug delivery technology and designed to be taken once at bedtime for the treatment of EDS or cataplexy in adults with narcolepsy.

In March 2020, Avadel completed the REST-ON trial, a randomized, double-blind, placebo-controlled, pivotal Phase 3 trial, to assess the efficacy and safety of FT218 in adults with narcolepsy. Among the three co-primary endpoints, FT218 demonstrated statistically significant and clinically meaningful results in EDS, the clinician's overall assessment of the patient's functioning, and reduction in cataplexy attacks for all three evaluated doses

compared to placebo.

In January 2018, the FDA granted FT218 Orphan Drug Designation for the treatment of narcolepsy based on the plausible hypothesis that FT218 may be clinically superior to the twice-nightly formulation of sodium oxybate already approved by the FDA for those with narcolepsy due to the consequences of middle-of-the-night dosing of the approved product. A marketing application for FT218 is currently under review by the FDA.

Avadel is currently evaluating the long-term safety and tolerability of FT218 in the open-label RESTORE clinical study. For more information, visit: www.restore-narcolepsy-study.com.

About Avadel Pharmaceuticals plc
Avadel Pharmaceuticals plc (Nasdaq: AVDL) is a biopharmaceutical company focused on transforming medicines to transform lives. Our approach includes applying innovative solutions to the development of medications that address the challenges patients face with current treatment options. Our current lead drug candidate, FT218, is an investigational formulation of sodium oxybate leveraging our proprietary drug delivery technology and designed to be taken once at bedtime for the treatment of EDS and cataplexy in adults with narcolepsy. For more information, please visit www.avadel.com.

Cautionary Disclosure Regarding Forward-Looking Statements
This press release includes "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. These forward-looking statements relate to our future expectations, beliefs, plans, strategies, objectives, results, conditions, financial performance, prospects, or other events. Such forward-looking statements include, but are not limited to, our expectations of the therapeutic benefits and tolerability of FT218, if approved. In some cases, forward-looking statements can be identified by the use of words such as "will," "may," "could," "believe," "expect," "look forward," "on track," "guidance," "anticipate," "estimate," "project," "next steps" and similar expressions, and the negatives thereof (if applicable).

Our forward-looking statements are based on estimates and assumptions that are made within the bounds of our knowledge of our business and operations and that we consider reasonable. However, our business and operations are subject to significant risks, and, as a result, there can be no assurance that actual results and the results of our business and operations will not differ materially from the results contemplated in such forward-looking statements. Factors that could cause actual results to differ from expectations in our forward-looking statements include the risks and uncertainties described in the "Risk Factors" section of Part I, Item 1A of our Annual Report on Form 10-K for the year ended December 31, 2021, which we filed with the Securities and Exchange Commission on March 16, 2022, and subsequent SEC filings.

Forward-looking statements speak only as of the date they are made and are not guarantees of future performance. Accordingly, you should not place undue reliance on forward-looking statements. We do not undertake any obligation to publicly update or revise our forward-looking statements, except as required by law.

Investor Contact:
Courtney Turiano
Stern Investor Relations, Inc.
Courtney.Turiano@sternir.com
(212) 698-8687

Media Contact:
Nicole Raisch Goelz
Real Chemistry
ngoelz@realchemistry.com
(408) 568-4292

References:

1. Basseti et al. European guideline and expert statements on the management of narcolepsy in adults and children. *Eur J Neurol*. 2021 Sep;28(9):2815-2830.

Source: Avadel Pharmaceuticals plc