Vanda Pharmaceuticals Accepts FDA Opportunity for a Hearing on New Drug Application for Tradipitant in Gastroparesis

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- *Highlights faulty FDA review*

WASHINGTON, Jan. 27, 2025 /PRNewswire/ -- Vanda Pharmaceuticals Inc. (Vanda) (Nasdaq: VNDA) today provides an update on the tradipitant development program.

Gastroparesis is a serious digestive disorder of the stomach. In patients with gastroparesis, food moves too slowly from the stomach to the small intestine, causing a host of gastrointestinal symptoms including nausea, vomiting, bloating, and abdominal pain. There has been no new drug approved by the FDA in more than 40 years and current treatments are often ineffective or not well tolerated. Unfortunately, it is difficult to study drugs for the treatment of gastroparesis, given the subjective variability of symptom severity and reporting, the variability of symptoms over time, and the spontaneous improvement of symptoms over time that contribute to large placebo responses. Drugs that have been tested in recent years have failed to overcome this placebo effect.

Vanda began studying tradipitant, a neurokinin 1 receptor antagonist, almost 10 years ago in patients with gastroparesis. To date, more than a thousand people have been treated with tradipitant, many of them for up to 3 months. Additionally, dozens of people are currently treated through an expanded access program, some of them for more than a year. Vanda has conducted two placebo-controlled studies and one open label study to study the efficacy and safety of tradipitant in gastroparesis. Because of the small patient population and uncomfortable symptoms, patient enrollment is a challenge, studies are difficult to conduct, and the overall program has taken almost ten years to complete.

In September of 2023 Vanda submitted a New Drug Application (NDA) seeking approval by the FDA. In September of 2024 the FDA rejected the application via a Complete Response Letter, suggesting that substantial evidence of efficacy was not established at this time. Vanda did not agree with this conclusion and requested through the Freedom of Information Act (FOIA) copies of the FDA reviews of the application, which Vanda has recently received.

The FDA is required by the federal Food, Drug, and Cosmetic Act (FDCA) to either approve an application in 180 days or give an opportunity for a hearing before the final decision on the application is rendered by the Secretary. The FDA did not follow this legal requirement, delayed the review by 6 months, and instead of an opportunity for a hearing, as mandated by the FDCA, issued a Complete Response Letter.

Nor is the FDA following the law now. By statute, once the FDA issues a proposal to refuse the approval of the application, the applicant must respond with whether they would like to have a hearing with the Commissioner. Even if an opportunity for a hearing is extended and accepted by the applicant, the FDA routinely denies the handful of these hearing requests in a summary judgement proceeding that is not outlined in the statute, without any hearing. The FDA has not had a hearing for an NDA for over 30 years.

The FDA has now published in the Federal Register conclusions from its review of Vanda's tradipitant application for the treatment of gastroparesis.

Below, Vanda explains the FDA's position, which is informed by the Notice of Opportunity for Hearing (NOOH) and the technical reviews that Vanda obtained through FOIA. Vanda focuses on the efficacy arguments.

The FDA disagreed that the clinical data submitted demonstrated substantial evidence of efficacy. Vanda submitted two studies, Study 1 and Study 2. In Study 1, (152 patients), tradipitant was shown to significantly improve the severity of nausea at week 4. In Study 2, (201 patients) both tradipitant and placebo showed improvements, but tradipitant, while numerically better, did not show a statistically significant difference from placebo.

In Study 1, Vanda's analysis showed changes in severity for nausea at week 4 equal to 1.25 and 0.73 points for tradipitant and placebo, respectively, and this difference was significant (p value = 0.0099). The FDA performed its own analysis that included 11 additional patients who were excluded, pursuant to the study protocol, for having only partial data (11 placebo and 2 on tradipitant) and reported very similar results, with changes in severity for nausea at week 4 equal to 1.20 and 0.79 points for tradipitant and placebo respectively and this difference was significant (p value = 0.0359).

In Study 2, Vanda reported changes in severity for nausea at week 12 equal to 1.55 and 1.49 points for tradipitant and placebo, respectively, and this difference was not significant (p value = 0.7411). The FDA performed its own analysis with similar results, with changes in severity for nausea at week 12 equal to 1.52 and 1.51 points for tradipitant and placebo respectively and this difference was not significant (p value = 0.9895).

Vanda conducted additional exploratory analyses for Study 2 to adjust for potential confounders such as baseline severity inflation and rescue medication use. These exploratory analyses showed that tradipitant was superior to placebo in reducing severity of nausea. The FDA disagreed with the validity and interpretation of these analyses.

The FDA also discounted other persuasive evidence that Vanda provided, including the efficacy evidence from a 600-patient open label study where tradipitant showed statistically significant improvements from baseline. Further, a statistically significant improvement was seen for patients with higher drug levels in their blood as compared to those with lower drug levels in their blood. The FDA also discounted the evidence from patients in the expanded access program, some treated for more than a year, who showed large improvement while on treatment, and often recurrence of symptoms during treatment interruptions due to FDA approval delays. The FDA similarly discounted the pooled analysis of the two studies that showed a significant effect of tradipitant, extending the significance beyond that seen in Study 1, because it said the results were driven by Study 1. The FDA similarly discounted other supportive evidence from other drugs with the same mechanism of action that improve chemotherapy and postoperative nausea and vomiting and discounted evidence from three placebo-controlled studies where tradipitant was shown to be effective in preventing vomiting associated with motion sickness.

The FDA agreed that Study 1 showed that tradipitant statistically significantly improved nausea severity as compared to placebo but still called this

evidence not persuasive, because in Study 2, the result was equivocal with both treatments showing a large but almost equal effect. For these reasons, the FDA concluded that the overall assessment of the evidence of efficacy did not meet the substantial evidence threshold.

Vanda disagrees with this assessment, and believes that the evidence provided meets the statutory standard of substantial evidence. Congress established the efficacy requirement for the approval of new drugs in 1962. Before that, only safety had to be shown. This addition was highly contested at the time and thus the law was written to require "substantial evidence" based on which an expert may conclude that the drug will have the effect it purports to have. Substantial evidence is a relatively low threshold of evidence. In the context of a civil lawsuit, the United States Supreme Court has explained that "[s]ubstantial evidence … means only such relevant evidence as a reasonable mind might accept as adequate to support a conclusion" and is not a "high" standard. *Biestek v. Berryhill*, 587 U.S. 97, 103 (2019).

The FDA agrees that the substantial evidence standard is "rather low", calling it "more than a scintilla" of evidence. *See* JA1306, *Vanda Pharms. Inc. v. FDA*, No. 24-1049 (D.C. Cir. 2024) (*FDA's Clinical Investigator Course*, presented by Dr. Robert Temple, M.D. (2013)). However, the FDA has interpreted the statutory requirement for "adequate and well controlled studies" to mean least two adequate and well controlled studies each one of them producing a significant "less than p=0.05" result. Additionally, the FDA thought that a federal court added another requirement on top of the statute that results also be "clinically meaningful." *Warner-Lambert Co. v. Heckler*, 787 F.2d 147 (3rd Cir. 1986). None of these requirements is consistent with the statutory language. Congress chose a specific standard of evidence for the efficacy of drugs, not because it would like to see ineffective drugs approved, but because a standard that is too high would erroneously lead to exclusion of otherwise useful and effective drugs. An evidentiary standard must be calibrated to minimize both false positives and false negatives: the substantial evidence standard does this.

The FDA has departed from Congress's standard and tipped that balance by adding the two-study requirement, the significance requirement, and the clinically meaningful requirement. Adhering to these requirements means that drugs that have only substantial evidence of efficacy will be rejected, contrary to the statutory text. And such a rejection can be very impactful, especially in a disorder like gastroparesis that has a serious unmet need and where no new drug has been approved in over 40 years. The question for the Commissioner is whether "a reasonable mind" of an expert may, after reviewing the tradipitant program's evidence for efficacy, conclude that the drug will be useful in improving nausea in gastroparesis, even if some other reasonable expert may conclude otherwise.

Today, Vanda accepted FDA's offer of an opportunity for a hearing. Under the statute, a hearing must commence within 120 days after receipt of the NOOH. Vanda hopes that, in break from prior practice, the FDA will adhere to this statutorily mandated time frame. Regardless, Vanda will continue to insist that the FDA apply proper legal criteria to Vanda's NDA to make its new therapy available to patients.

About Vanda Pharmaceuticals Inc.

Vanda is a leading global biopharmaceutical company focused on the development and commercialization of innovative therapies to address high unmet medical needs and improve the lives of patients. For more on Vanda Pharmaceuticals Inc., please visit www.vandapharma.com and follow us on Twitter @vandapharma.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Various statements in this press release, including, but not limited to statements regarding the timing of a hearing on the tradipitant data, Vanda's intention to require the FDA to apply proper legal criteria to the review of its NDA for tradipitant and the availability of tradipitant to treat patients with gastroparesis, are "forward-looking statements" under the securities laws. All statements other than statements of historical fact are statements that could be deemed forward-looking statements. Forward-looking statements are based upon current expectations and assumptions that involve risks, changes in circumstances and uncertainties. Important factors that could cause actual results to differ materially from those reflected in Vanda's forward-looking statements include, among others,the FDA's adherence to the statutorily mandated time frame for commencing a hearing, the FDA's willingness to apply the statutorily prescribed standard of review in evaluating Vanda's NDA and the FDA's ultimate determination as to the approvability of tradipitant for the treatment of gastroparesis. Therefore, no assurance can be given that the results or developments anticipated by Vanda will be realized, or even if substantially realized, that they will have the expected consequences to, or effects on, Vanda. Forward-looking statements in this press release should be evaluated together with the various risks and uncertainties that affect Vanda's business and market, particularly those identified in the "Cautionary Note Regarding Forward-Looking Statements", "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of Vanda's most recent Annual Report on Form 10-K, as updated by Vanda's subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the U.S. Securities and Exchange Commission, which are available at www.sec.gov.

All written and verbal forward-looking statements attributable to Vanda or any person acting on its behalf are expressly qualified in their entirety by the cautionary statements contained or referred to herein. Vanda cautions investors not to rely too heavily on the forward-looking statements Vanda makes or that are made on its behalf. The information in this press release is provided only as of the date of this press release, and Vanda undertakes no obligation, and specifically declines any obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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