Vanda Pharmaceuticals Announces Tradipitant Phase II Proof of Concept Study Results for Chronic Pruritus in Atopic Dermatitis

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- Tradipitant and placebo both showed significant improvements from baseline
- No significant effect differences seen between treatment groups due to high placebo effect
- Pharmacokinetic analysis revealed a significant and distinct exposure response relationship to treatment with tradipitant
- Subset analysis revealed significant differences between tradipitant and placebo on a number of pruritus related endpoints

WASHINGTON, March 4, 2015 /PRNewswire/ -- Vanda Pharmaceuticals Inc. (Vanda) (NASDAQ: VNDA) today announced top-line results of the Phase II proof of concept clinical study investigating the safety and efficacy of tradipitant as a monotherapy in the treatment of chronic pruritus in patients with atopic dermatitis. Despite a highly significant and clinically meaningful improvement from baseline by tradipitant (40.5mm improvement from baseline, $p<0.0001$) as measured on a 100mm unit Visual Analog Scale (VAS) for itch, a very high placebo effect (36.5 mm improvement from baseline, $p<0.0001$) on the change from baseline led to no statistical difference from placebo. However, subsequent analysis of population PK samples across all patients in the study revealed significant and clinically meaningful responses across multiple outcomes evaluated in individuals with higher levels of tradipitant exposure at the time of their pruritus assessments.

"The results of this exploratory study are encouraging and promising; a target-specific therapy using an NK-1 receptor antagonist in severe atopic dermatitis pruritus is a novel concept and will help AD patients suffering from the symptom worldwide," said Dr. Sonja Staender, Department of Dermatology, and Head of the Interdisciplinary Competence Center Chronic Pruritus (KCP) of the University Hospital in Munster, Germany.

Tradipitant, formerly known as VLY-686, is a neurokinin 1 receptor antagonist under clinical investigation for the treatment of chronic pruritus in patients with atopic dermatitis. The pre-specified primary endpoint of the Phase II proof of concept clinical study was the change from baseline on the Visual Analog Scale (VAS) for itch. Due to high placebo effect, there was no significant difference from placebo on this pre-specified endpoint, however, Vanda believes this proof of concept study was informative, in that through subsequent analyses, it has discovered an exposure response relationship and further observed a significant and clinically meaningful response across several pruritus related outcomes evaluated in individuals with higher blood plasma levels of tradipitant. This is not unexpected given that all the assessments related to pruritus are significantly associated with the itch sensation the patient is experiencing at that time. Based on the data Vanda examined across the study, lower blood plasma levels of tradipitant may be below a threshold of efficacy to ameliorate the itch sensation in patients.

About Chronic Pruritus

Chronic pruritus affects millions of people worldwide and represents a serious and unmet medical need. The itch sensation is believed to be induced at least in part through the action of the endogenous neuropeptide substance P, through the binding at NK-1Rs expressed on multiple skin cells.

VP-VLY-686-2101 Study

In the Phase II proof of concept clinical study (VP-VLY-686-2101), Vanda studied the effects of tradipitant in chronic pruritus in patients with atopic dermatitis. Patients with a VAS score of greater than 70mm during one of the two days preceding inclusion into the study were randomized to receive orally either 100 mg of tradipitant (N=34) or placebo (N=35) once a day in the evening. Baseline VAS scores were 76.1 and 77.2 for the tradipitant and placebo arms respectively. Patients received treatment for 4 weeks and efficacy was evaluated through a number of clinical research instruments. In addition, at the time of efficacy evaluation blood samples were collected for PK analysis in order to determine the plasma levels of tradipitant.

A PK-PD analysis in the tradipitant treatment arm showed a significant correlation between blood levels of tradipitant and the VAS change from baseline ($p<0.05$). Individuals with higher circulating levels of tradipitant at the time of the efficacy evaluation demonstrated higher magnitude of response. A separate PK analysis of the time of pruritus assessment revealed that approximately half the patients in the study came in for morning (AM group, ~12 hours post-dose) visits for their pruritus assessments and that these patients also had higher blood levels of tradipitant than those who came in the afternoon (PM group, ~18 hours post-dose).

A further analysis of the AM group revealed significant and clinically meaningful effects of tradipitant as compared to placebo and is shown in the table below. Higher concentrations of tradipitant were associated with higher efficacy in treating chronic pruritus in the study. A similar analysis in the PM group showed no significant differences between tradipitant and placebo.

Table 1. AM group efficacy analysis of pruritus measures

Endpoint	Tradipitant N=18	Placebo N=17	Diff	P-value
VAS change (mm)	-54.0	-30.3	-24.7	< 0.01
VRS change	-1.46	-0.67	-0.79	< 0.05
CGI-C	2.46	3.61	-1.15	< 0.05
PBI	1.47	0.73	0.74	< 0.05
SCORAD subjective	-9.58	-4.36	-5.23	< 0.01

This data is consistent with the hypothesis that tradipitant, an NK-1R antagonist, may offer symptomatic relief in patients with pruritus (VAS, VRS,

SCORAD subjective). Endpoints were also collected in the study that correspond to the underlying disease (SKINDEX, SCORAD objective, EASI and DLQI). These results did not show any significant difference from placebo which would be expected from a drug targeting the symptom of itch in a short-term 4-week study. Importantly, as pruritus, the intractable itching associated with atopic dermatitis, is the major complaint of patients, the effects that were also seen in the CGI-C scale and the PBI scales suggest a recognizable overall clinically meaningful effect from both the clinician and the patient perspective.

"These findings of the effects of tradipitant in improving chronic itching in patients with atopic dermatitis are encouraging and, if confirmed in future studies, they may represent a significant medical advance in treating these patients," said Mihael H. Polymeropoulos, M.D., Vanda's President and CEO.

In conclusion, while the study failed to show an overall effect of the predefined dose of tradipitant for this study, primarily due to the large placebo effect, the study demonstrated a PK-response relationship as well as significant benefits in the group of patients that were evaluated at the time of higher blood concentrations of tradipitant. However, given the exploratory nature of these analyses in this proof of concept study, additional studies may be required to further confirm these findings. In this study tradipitant 100 mg was well-tolerated and the adverse event profile was mild and similar to placebo.

About Tradipitant

Tradipitant is an NK-1R antagonist licensed by Vanda from Eli Lilly and Company (Lilly) in April 2012. Tradipitant (formerly known at Lilly as LY686017 and at Vanda as VLY-686) is currently in clinical development for chronic pruritus in patients with atopic dermatitis. Previous research at Lilly focused on the potential of tradipitant as a novel therapeutic in alcohol dependence (1). The patent describing tradipitant as a new chemical entity expires worldwide in April 2023, except in the United States, where it expires in June 2024, absent any applicable patent term adjustments.

About the Neurokinin-1 Receptor and Substance P

The NK-1R is expressed throughout different tissues of the body, with major activity found in neuronal tissue. SP and NK-1R interactions in neuronal tissue regulate neurogenic inflammation locally and the pain perception pathway through the central nervous system. Other tissues, including endothelial cells and immune cells, have also exhibited SP and NK-1R activity (2). The activation of NK-1R by the natural ligand SP is involved in numerous physiological processes, including the perception of pain, behavioral stressors, cravings, and the processes of nausea and vomiting (1,2,3). An inappropriate over-expression of SP either in nervous tissue or peripherally could result in pathological conditions such as substance dependence, anxiety, nausea/vomiting, and pruritus (1,2,3,4). An NK-1R antagonist may possess the ability to reduce this over-stimulation of the NK-1R, and as a result address the underlying pathophysiology of the symptoms in these conditions.

About Vanda

Vanda Pharmaceuticals Inc. is a biopharmaceutical company focused on the development and commercialization of products for the treatment of central nervous system disorders. For more on Vanda, please visit www.vandapharma.com.

Abbreviations

AD	Atopic Dermatitis
CGI-C	Clinical Global Impression of Change
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
NK-1R	Neurokinin-1 Receptor
PBI	Patient Benefit Index
PD	Pharmacodynamics
PK	Pharmacokinetic
SCORAD	SCORing Atopic Dermatitis Index
SKINDEX	A Brief Quality-of-Life Measure for Patients with Skin Diseases
SP	Substance P
VAS	Visual Analog Scale
VRS	Verbal Rating Scale

References

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CAUTIONARY NOTE REGARDING FORWARD LOOKING STATEMENTS

Various statements in this release are "forward-looking statements" under the securities laws. Forward-looking statements are based upon current expectations that involve risks, changes in circumstances, assumptions and uncertainties. Important factors that could cause actual results to differ materially from those reflected in Vanda's forward-looking statements include, among others: Vanda's belief that NK-1R inhibition may be of benefit in the treatment of chronic pruritus in patients with atopic dermatitis, the results of Vanda's clinical development activities of tradipitant, delays in the completion of Vanda's clinical trials of tradipitant; a failure of tradipitant to be demonstrably safe and effective; and other factors that are described in the "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" sections of Vanda's annual report

on Form 10-K for the fiscal year ended December 31, 2013 and quarterly report on Form 10-Q for the quarter ended September 30, 2014, which are on file with the SEC and available on the SEC's website at www.sec.gov. Additional factors may also be set forth in those sections of Vanda 's annual report on Form 10-K for the fiscal year ended December 31, 2014 to be filed with the SEC in the first quarter of 2015. In addition to the risks described above and in Vanda's annual report on Form 10-K and quarterly reports on Form 10-Q, other unknown or unpredictable factors also could affect Vanda's results. There can be no assurance that the actual 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. Therefore, no assurance can be given that the outcomes stated in such forward-looking statements and estimates will be achieved.

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 release is provided only as of the date of this 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.

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