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# Theravance Biopharma Presents Positive Results From a Preclinical Colitis Model for TD-1473, a GI-Targeted Pan-Janus Kinase (JAK) Inhibitor

## Presentations at 11th Congress of ECCO Showed TD-1473 to Be a Potent and Selective Pan-JAK Inhibitor Capable of Achieving High Colonic Drug Levels and Reduced Colitis-Related Disease Activity Without Significant Systemic Exposure Following Oral Dosing in a Preclinical Model

DUBLIN, IRELAND -- (Marketwired) -- 03/18/16 -- Theravance Biopharma, Inc. (NASDAQ: TBPH) ("Theravance Biopharma" or the "Company") today announced that positive preclinical study results for TD-1473, a novel, potent, orally administered GI-targeted pan-Janus kinase (JAK) inhibitor, were presented today at the 11$^{th}$ Congress of the European Crohn's and Colitis Organisation (ECCO) in Amsterdam. The Company is developing TD-1473 as an investigational compound with the potential to treat a range of inflammatory intestinal diseases, including ulcerative colitis.

The study showed TD-1473 to be a potent and selective pan-JAK inhibitor capable of achieving high colonic drug levels without significant systemic exposure following oral dosing in a preclinical animal model. The study also demonstrated that TD-1473 was effective in reducing markers of colitis-related disease activity without suppressing systemic immune cells. In the same study, another JAK inhibitor (tofacitinib, currently in clinical development for moderate to severe ulcerative colitis) showed similar reductions in disease activity, but with higher concentrations of drug in the plasma than in the colon, and with evidence of systemic immune suppression.

"We view these results as strong foundational support from which to advance the TD-1473 program. The preclinical data suggest that systemic inhibition of JAK is not required to treat inflammation in the wall of the colon," said Brett Haumann, M.D., Chief Medical Officer at Theravance Biopharma. "Our research approach has been to develop targeted JAK inhibitors with anti-inflammatory activity that is limited specifically to the GI tract and reduces the risk of systemic side effects. Ulcerative colitis is a very debilitating disease affecting roughly 700,000 patients in the United States, and our vision is to develop a treatment option with a more favorable benefit/risk profile than current therapies. We look forward to further supplementing our scientific research of TD-1473 with the insights we gain from our ongoing Phase 1 clinical trial in healthy volunteers, which is expected to be completed during the first half of this year. Assuming a positive outcome from that trial, we then intend to initiate a Phase 1b study in the second half of the year."

*Comparing Preclinical Properties of TD-1473 and Tofacitinib*

In one study, the preclinical properties of TD-1473, an oral pan-JAK inhibitor with activity that is specifically targeted to the inflamed wall of the GI tract, were compared to that of tofacitinib, an oral pan-JAK inhibitor with broad systemic exposure and activity. Data showed that both compounds behaved as potent pan-JAK inhibitors and were effective in reducing disease activity, using a number of measures of colonic inflammation similar to those seen in patients with ulcerative colitis. However, at doses providing similar reductions in disease activity, the ratio of drug in the systemic circulation versus the colon was much lower for TD-1473 than that of tofacitinib, and in contrast to tofacitinib, TD-1473 had no effect on systemic immune cells, demonstrating the GI-targeted activity of TD-1473.

*Therapeutic Potential of Targeted vs. Systemic JAK Inhibition in Colitis*

A second study compared the therapeutic potential of colon-targeted JAK inhibition to systemic JAK inhibition in a preclinical colitis model. Researchers showed that administration of tofacitinib directly into the colon (1 mg/kg BID) achieved similar reductions in colitis-related disease activity as orally dosed tofacitinib (15 mg/kg BID). These two routes of administration achieved similar levels of colonic exposure of tofacitinib, but the oral dose resulted in significantly higher systemic exposure. These findings suggest that a GI-targeted JAK inhibitor may provide clinical efficacy in the treatment of colitis and other inflammatory intestinal diseases without the need for high systemic exposure and the attendant risk of systemically-mediated adverse effects.

***About TD-1473***

TD-1473 is an internally discovered JAK inhibitor that has demonstrated a high affinity for each of the JAK family of enzymes (JAK1, JAK2, JAK3 and TYK2). Through the inhibition of these enzymes, TD-1473 interferes with the JAK/STAT signaling pathway and, in turn, modulates the activity of a wide range of pro-inflammatory cytokines. Importantly, TD-1473 is a GI-

targeted treatment specifically designed to distribute to the tissues of the GI tract and to minimize systemic exposure.

The Company is currently conducting a randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) Phase 1 study of TD-1473 in healthy subjects, which is expected to be completed during the first half of 2016. The primary objective of the study is the evaluation of the safety and tolerability of single ascending doses and multiple ascending doses of TD-1473 in healthy subjects. A key secondary objective of the trial will be the characterization of pharmacokinetics related to TD-1473, which will help determine the amount of TD-1473 that enters systemic circulation following oral administration. Assuming positive results from the ongoing study, the Company intends to initiate a Phase 1b trial of TD-1473 in the second half of 2016.

***About Theravance Biopharma***

Theravance Biopharma is a diversified biopharmaceutical company with the core purpose of creating medicines that make a difference in the lives of patients suffering from serious illness. Our pipeline of internally discovered product candidates includes potential best-in-class medicines to address the unmet needs of patients being treated for serious conditions primarily in the acute care setting. VIBATIV® (telavancin), our first commercial product, is a once-daily dual-mechanism antibiotic approved in the U.S., Europe and certain other countries for certain difficult-to-treat infections. Revefenacin (TD-4208) is a long-acting muscarinic antagonist (LAMA) being developed as a potential once-daily, nebulized treatment for chronic obstructive pulmonary disease (COPD). Our neprilysin (NEP) inhibitor program is designed to develop selective NEP inhibitors for the treatment of a range of major cardiovascular and renal diseases, including acute and chronic heart failure, hypertension and chronic kidney diseases such as diabetic nephropathy. Our research efforts are focused in the areas of inflammation and immunology, with the goal of designing medicines that provide targeted drug delivery to tissues in the lung and gastrointestinal tract in order to maximize patient benefit and minimize risk. The first program to emerge from this research is designed to develop GI-targeted pan-Janus kinase (JAK) inhibitors for the treatment of a range of inflammatory intestinal diseases. In addition, we have an economic interest in future payments that may be made by Glaxo Group Limited or one of its affiliates pursuant to its agreements with Innoviva, Inc. relating to certain drug development programs, including the Closed Triple (the combination of fluticasone furoate, umeclidinium, and vilanterol).

For more information, please visit www.theravance.com.



*This press release contains certain "forward-looking" statements as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding, among other things, statements relating to goals, plans, objectives and future events. Theravance Biopharma intends such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. Examples of such statements include statements relating to: the Company's strategies, plans and objectives, the Company's regulatory strategies and timing and results of clinical studies, the potential benefits and mechanisms of action of the Company's product and product candidates and the Company's expectations for product candidates through development and commercialization. These statements are based on the current estimates and assumptions of the management of Theravance Biopharma as of the date of the press release and are subject to risks, uncertainties, changes in circumstances, assumptions and other factors that may cause the actual results of Theravance Biopharma to be materially different from those reflected in the forward-looking statements. Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements include, among others, risks related to: delays or difficulties in commencing or completing clinical studies, the potential that results from clinical or non-clinical studies indicate the Company's product candidates are unsafe or ineffective, the feasibility of undertaking future clinical trials for our product candidates based on FDA policies and feedback, dependence on third parties to conduct clinical studies, delays or failure to achieve and maintain regulatory approvals for product candidates, risks of collaborating with third parties to discover, develop and commercialize product and product candidates and risks associated with establishing and maintaining sales, marketing and distribution capabilities with appropriate expertise and supporting infrastructure. Other risks affecting Theravance Biopharma are described under the heading "Risk Factors" contained in Theravance Biopharma's Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 11, 2016. In addition to the risks described above and in Theravance Biopharma's other filings with the SEC, other unknown or unpredictable factors also could affect Theravance Biopharma's results. No forward-looking statements can be guaranteed and actual results may differ materially from such statements. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Theravance Biopharma assumes no obligation to update its forward-looking statements on account of new information, future events or otherwise, except as required by law.*

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