

## **Theravance Biopharma Reports Encouraging Data from First Cohort of Patients in Phase 1b Clinical Trial of TD-1473 in Ulcerative Colitis**

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### **Evidence of Localized Target Engagement after Four Weeks of Treatment Minimal Systemic Exposure No Evidence of Systemic Immunosuppression or Infections Company Plans to Progress TD-1473 into Induction and Maintenance Study in 2018**

DUBLIN, Aug. 8, 2017 /PRNewswire/ -- Theravance Biopharma, Inc. (NASDAQ: TBPH) ("Theravance Biopharma" or the "Company") today announced early evidence of localized target engagement from the Company's ongoing Phase 1b clinical trial of TD-1473 in patients with moderate to severe active ulcerative colitis. TD-1473 is a novel, potent, orally administered and intestinally restricted pan-Janus kinase (JAK) inhibitor in clinical development, with the potential to treat a range of inflammatory intestinal diseases. In contrast to other oral JAK inhibitors under development for inflammatory bowel disease, TD-1473 is specifically designed to act directly at the site of inflammation in the intestinal wall with minimal systemic exposure.

Theravance Biopharma Logo

The Phase 1b exploratory study is designed to evaluate the safety, tolerability, and pharmacokinetics (PK) of TD-1473 over a 28-day treatment period. In addition, the study incorporates biomarker analysis and clinical, endoscopic, and histologic assessments to evaluate biological effect. The first cohort of patients included 10 patients receiving 80 mg of TD-1473 once daily for 28 days and three receiving matched placebo.

Data from the first cohort of patients demonstrated encouraging evidence of localized biological activity for TD-1473 and included the following:

- Minimal systemic exposure of TD-1473 based on evaluation of plasma levels, consistent with data seen in a previously conducted Phase 1 study of healthy volunteers
- No evidence of systemic immunosuppression or infections, including no occurrences of zoster reactivation. In addition, no alterations in total leukocytes, neutrophils, or lymphocytes in patients receiving TD-1473, relative to patients receiving placebo
- 7 of 10 patients receiving TD-1473 experienced ? 1-point reduction in Mayo rectal bleeding subscore<sup>1</sup>, compared to 1 of 3 patients receiving placebo
- 3 of 10 patients receiving TD-1473 experienced ? 1-point reduction in Mayo endoscopic subscore<sup>1</sup> (assessed by central reading), compared to none of the patients receiving placebo
- 2 of 10 patients receiving TD-1473 showed evidence of mucosal healing, based on Mayo endoscopic subscore<sup>1</sup>, compared to none of the patients receiving placebo
- 2 of 10 patients receiving TD-1473 achieved clinical response by total Mayo Score<sup>1</sup>, compared to none of the patients receiving placebo
- 4 of 10 patients receiving TD-1473 achieved clinical response by partial Mayo score<sup>1</sup>, compared to 1 of 3 patients receiving placebo
- Reductions in serum C-reactive protein (CRP) and fecal calprotectin (FC), two surrogate biomarkers for ulcerative colitis, in patients receiving TD-1473
- Reduction in levels of phosphorylated signal transducer and activator of transcription 1 (pSTAT1), indicative of diminished cytokine activity, in tissue biopsies from patients receiving TD-1473

"In a small Phase 1b trial not statistically powered to demonstrate efficacy, it is remarkable to see compelling directional change in local biological effect for patients receiving TD-1473, particularly a change in rectal bleeding and endoscopic subscores. Further, these effects were measured after just four weeks of treatment, a timeframe shorter than the typical induction endpoint in ulcerative colitis trials," said William Sandborn, MD, Chief of the Division of Gastroenterology of University of California, San Diego Health. "These early signals of efficacy with limited levels of systemic exposure position TD-1473 as a promising potential treatment for ulcerative colitis."

In the first cohort, there were no moderate or serious adverse events related to TD-1473, and the only adverse events reported in patients dosed with TD-1473 were considered mild in severity, with none leading to study discontinuation. Furthermore, evaluations of chemistry and hematologic parameters typically affected by systemically active JAK inhibitors, including natural killer cells and lipid levels, showed no alterations relative to placebo.

"These data provide encouraging initial evidence of TD-1473's clinical activity in our first cohort of ulcerative colitis patients. In addition to seeing improvements in measurements of disease activity within four weeks of treatment, we have seen minimal systemic exposure and a favorable tolerability profile that is consistent with the desired target product profile," said Brett Haumann, MD, Chief Medical Officer of Theravance Biopharma. "The body of evidence from the first cohort of this study suggest both that TD-1473 was restricted to, and biologically active at, the target disease location within the intestinal tract with minimal absorption into the systemic circulation and that active intestinal inflammation does not lead to increased systemic exposure of TD-1473."

Top-line results from the entire Phase 1b study will be available following completion of the two remaining cohorts, with an objective of evaluating both a higher and lower dose of TD-1473 in ulcerative colitis patients. On the basis of the encouraging data generated in the first cohort of patients, the Company plans to progress TD-1473 into a larger induction and maintenance study in 2018.

#### **About the Phase 1b Study**

The ongoing Phase 1b trial of TD-1473 is a multi-center, randomized, double-blind, multi-dose, placebo-controlled study in 40 patients with moderate to severe active ulcerative colitis. Three doses of TD-1473 (80, 20, and 270 mg) are being evaluated versus placebo. The primary objectives of the study are to evaluate the safety and tolerability of TD-1473 administered for 28 days, as well as to assess the compound's plasma exposure following administration. Secondary objectives

of the study include the evaluation of the effect of TD-1473 on ulcerative colitis disease activity through biomarker analysis and clinical, endoscopic, and histologic assessments.

### **About Intestinally Restricted Pan-Janus (JAK) Kinase Inhibition**

JAK inhibitors function by inhibiting the activity of one or more of the Janus kinase family of enzymes (JAK1, JAK2, JAK3, TYK2) that play a key role in cytokine signaling. Inhibiting these JAK enzymes interferes with the JAK/STAT signaling pathway and, in turn, modulates the activity of a wide range of pro-inflammatory cytokines. JAK inhibitors are currently approved for the treatment of diseases such as rheumatoid arthritis and myelofibrosis, and have demonstrated therapeutic benefit for patients with ulcerative colitis. However, these products are known to have side effects associated with systemic exposure.

TD-1473 is an internally-discovered JAK inhibitor that has demonstrated a high affinity for each of the JAK family of enzymes. Importantly, TD-1473 is an intestinally restricted treatment specifically designed to distribute adequately and predominantly to the tissues of the intestinal tract, treating inflammation in those tissues while minimizing systemic exposure. Theravance Biopharma is focused on utilizing targeted JAK inhibitors for potential treatment of a range of inflammatory intestinal diseases including ulcerative colitis, which affects roughly 700,000 patients in the United States.

### **About Theravance Biopharma**

Theravance Biopharma is a diversified biopharmaceutical company with the core purpose of creating medicines that help improve 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<sup>®</sup> (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. Revedfenacin (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 intestinal tract in order to maximize patient benefit and minimize risk. The first program to emerge from this research is designed to develop intestinally restricted 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 (GSK) 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), currently in development for the treatment of COPD and asthma.

For more information, please visit [www.theravance.com](http://www.theravance.com).

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*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, expectations 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 of clinical studies, the potential benefits and mechanisms of action of the company's product and product candidates, the company's expectations for product candidates through development, potential regulatory approval and commercialization (including their potential as components of combination therapies) and the company's expectations for product sales. 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 (including when our product candidates are studied in combination with other compounds), 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 or relying on 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 technical expertise and supporting infrastructure. Other risks affecting Theravance Biopharma are described under the heading "Risk Factors" contained in Theravance Biopharma's Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 9, 2017 and Theravance Biopharma's other filings with the SEC. In addition to the risks described above and in Theravance Biopharma's 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.*

### **References:**

<sup>1</sup> Gastroenterology Vol. 148, No. 1, pages 37-51. "Converging Goals of Treatment of Inflammatory Bowel Disease From Clinical Trials and Practice." Barrett G. Levesque, William J. Sandborn, Joannie Ruel, Brian G. Feagan, Bruce E. Sands, and Jean-Frederic Colombel. [http://www.gastrojournal.org/article/S0016-5085\(14\)00999-8/pdf](http://www.gastrojournal.org/article/S0016-5085(14)00999-8/pdf) Published online August 12, 2014. Mayo Clinic Score (MCS) as referenced herein, with endoscopic subscore modified such that mild friability is scored as a 2 rather than a 1 (pages 39-40). Clinical response for partial MCS consistent with clinical response for MCS, except criteria for clinical response by partial MCS include a decrease in partial MCS of at least 2 points versus 3 points in the MCS criteria.

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