Theravance Biopharma Reports Data from Phase 1b Study of TD-1473 in Oral Presentation at Digestive Disease Week (DDW) 2019

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Data Demonstrate Signals of Clinical, Histologic and Biomarker Activity Suggesting Localized Target Engagement following Four Weeks of Treatment in Patients with Moderately-to-Severely Active Ulcerative Colitis

Additional Findings Demonstrate Minimal Systemic Exposure and No Evidence of Systemic Immunosuppression or Systemic Infections following TD-1473 Treatment, Highlighting Potential Differentiation for Gut-Selective Pan-JAK Inhibitor as Compared to Systemically Active JAK Inhibitors

DUBLIN, Ireland, May 21, 2019 /PRNewswire/ -- Theravance Biopharma, Inc. (NASDAQ: TBPH) ("Theravance Biopharma" or the "Company") today reported data from the exploratory Phase 1b study of the gut-selective pan-Janus kinase (JAK) inhibitor, TD-1473, in an oral presentation at Digestive Disease Week (DDW) 2019. Presented data demonstrated that four weeks of TD-1473 treatment produced signals of clinical, histologic, and biomarker activity, suggesting the achievement of localized target engagement in patients with moderately-to-severely active ulcerative colitis (UC). Additionally, in this study, data demonstrated minimal systemic exposures and suggested no evidence of systemic immunosuppression or systemic opportunistic infections associated with the gut-selective compound. This localization of biological activity within the target organ highlights potential differentiation for TD-1473 as compared to systemically active JAK inhibitors on the market or in development, which have been associated with dose-limiting toxicity. DDW 2019 is being held May 18-21, 2019 in San Diego, CA.

The Phase 1b exploratory study was designed to evaluate the safety and pharmacokinetics (PK) of TD-1473 over a 28-day treatment period. In addition, although not powered for these observations, the study incorporated biomarker analysis and clinical, endoscopic, and histologic assessments as exploratory endpoints to evaluate biological effect. The trial enrolled 40 patients across four treatment arms: placebo (n=9); TD-1473 20 mg/daily (n=10); TD-1473 80 mg/daily (n=10); and, TD-1473 270 mg/daily (n=11).

Study results presented at DDW 2019 include:

Clinical Response Rate and Mucosal Healing:

- Numerically higher rates of clinical response were observed for TD-1473 after four weeks of treatment as compared to placebo. Clinical response, which was defined as a reduction in total Mayo score of ≥ 3 points and ≥ 30%, with a reduction in rectal bleeding subscore by ≥ 1 point or an absolute rectal bleeding subscore of ≤ 1 point, was achieved by 2 of 10 patients (20%) in the 20 mg cohort, 2 of 10 patients (20%) in the 80 mg cohort, and 6 of 11 patients (55%) in the 270 mg cohort, compared to 1 of 9 patients (11%) in placebo group.
- Numerically higher rates of mucosal healing were observed for TD-1473 after four weeks of treatment as compared to placebo. Mucosal healing, categorized as having an endoscopic subscore ≤ 1, was achieved by 2 of 10 patients (20%) in the 20 mg cohort, 2 of 10 patients (20%) in the 80 mg cohort, and 1 of 11 patients (9%) in the 270 mg cohort, compared to 0 of 9 patients (0%) in placebo group.

Endoscopic and Rectal Bleeding Improvements:

- Numerically higher rates of endoscopy improvement were observed for TD-1473 after four weeks of treatment as compared to placebo. Endoscopic improvement, which was defined as a ≥ 1-point reduction in Mayo endoscopic subscore[1] (assessed by central reading), was achieved by 2 of 10 patients (20%) in the 20 mg cohort, 3 of 10 patients (30%) in the 80 mg cohort, and 2 of 11 patients (18%) in the 270 mg cohort, compared to 0 of 9 patients (0%) in placebo group.
- Numerically higher rates of improvement in rectal bleeding were observed for TD-1473 in the 80 mg and 270 mg cohorts after four weeks of treatment as compared to placebo. Rectal bleeding improvement, which was defined as a ≥ 1-point reduction in Mayo rectal bleeding subscore[1], was achieved by 3 of 10 patients (30%) in the 20 mg cohort, 7 of 10 patients (70%) in the 80 mg cohort, and 8 of 11 patients (73%) in the 270 mg cohort, compared to 4 of 9 patients (44%) in placebo group.

Histologic Improvements:

- Histologic activity was measured using the Robarts Histopathology Index (RHI), a histologic scoring system ranging from 0

(no UC disease activity) to 33 (severe UC disease activity). Patients in the 20 mg and 270 mg cohorts demonstrated average reductions in RHI score from baseline of 4.5 points and 5.3 points, respectively. This compared to an average RHI score reduction of 2.0 points from baseline in the placebo group.

Surrogate Inflammatory Biomarkers:

- Placebo-adjusted reductions in serum C-reactive protein (CRP) were seen in all TD-1473 cohorts, ranging from 57% to 70%.
- Placebo-adjusted reductions in fecal calprotectin (FC) were seen in the 80 mg and 270 mg cohorts, ranging from 26% to 31%.

Evidence of Gut-Selective Activity:

- Minimal systemic exposure to TD-1473 based on evaluation of plasma levels, consistent with data seen in a previously conducted Phase 1 study of healthy volunteers.
- Colonic tissue concentrations of TD-1473 were higher than plasma at respective dose levels and at or above those predicted to be required for localized JAK inhibition at the site of inflammation in the 80 mg and 270 mg cohorts.
- No evidence of systemic immunosuppression, as reflected by no alterations in total leukocytes, neutrophils, or lymphocytes in patients receiving TD-1473, relative to patients receiving placebo.

Safety:

- TD-1473 was generally well tolerated in the study with no adverse events leading to study drug interruption or discontinuation. There were two serious adverse events (20 mg and 80 mg) which were characterized as hospitalizations for UC exacerbations, deemed by the reporting investigators as not related to study drug. There were no serious infections, tuberculosis or other opportunistic infections, bowel perforations, or herpes zoster. Additionally, there were no meaningful changes in hepatic, renal, lipid, or hematologic laboratory parameters.

"The totality and consistency of these data across a broad range of clinical, histologic and biomarker measures of UC disease activity after just four weeks of treatment is quite encouraging, despite the small number of patients enrolled in the study," said William Sandborn, MD, chief of the division of gastroenterology of University of California, San Diego Health and presenter of the TD-1473 data at DDW 2019. "Also promising is the clear evidence pointing to the fact that the biologic activity of the compound is contained almost exclusively within the gut. As such, we see only minimal systemic exposure and no evidence of the troubling systemic JAK inhibition that has been linked to dose-limiting toxicities with other compounds in this therapeutic class that lack organ selectivity. These results suggest that TD-1473 may represent an important new type of JAK inhibitor, capable of delivering the powerful therapeutic potential of this important class with potentially less concern for systemic adverse effects due to its gut-selective design."

"Systemically active JAK inhibitors have been shown to be effective in treating inflammatory diseases, but continue to be challenged by dose-limiting side effects that prevent such therapies from being used at the optimal dose. Theravance Biopharma's strategic focus is on designing and developing pan-JAK inhibitors that are organ-selective, treating inflammation only in the organ of interest. TD-1473 exemplifies this approach as a gut-selective therapy designed to treat inflammatory bowel diseases," said Brett Haumann, MD, chief medical officer at Theravance Biopharma. "Whereas others are now focused on trying to solve the challenges of systemic JAK inhibition by only targeting a single JAK enzyme, we are attempting to avoid that problem altogether by restricting the pan-JAK activity of TD-1473 to the intestinal wall. In avoiding the side effects seen with other therapies, we believe our organ-selective approach can broaden the therapeutic window significantly, allowing us to dose at a level that achieves maximum therapeutic benefit. We look forward to continuing our TD-1473 development program and generating additional clinical data in our current Phase 2 and Phase 3 programs to support what we believe may become a best-in-class therapeutic and safety profile."

TD-1473 is a novel, orally administered and gut-selective pan-JAK inhibitor in clinical development with the potential to treat a range of inflammatory intestinal diseases, including ulcerative colitis and Crohn's disease. In contrast to other oral JAK inhibitors under development for inflammatory bowel disease, TD-1473 is specifically designed to act locally at the site of inflammation in the intestinal wall thereby limiting systemic exposure.

Theravance Biopharma is currently evaluating TD-1473 in Phase 2b/3 induction and maintenance studies in moderately-to-severely active ulcerative colitis and a Phase 2 clinical trial in patients with moderately-to-severely active Crohn's disease.

About Theravance Biopharma and Janssen Strategic Collaboration

Theravance Biopharma and Janssen Biotech, Inc. have a global co-development and commercialization agreement for TD-1473 and related back-up compounds for inflammatory intestinal diseases, including ulcerative colitis and Crohn's disease. Under the terms of the agreement, Theravance Biopharma received an upfront payment of $100 million and is eligible to receive up to an additional $900 million in potential payments, if Janssen elects to remain in the collaboration following the completion of certain Phase 2 activities. Theravance Biopharma together with Janssen will jointly develop and commercialize TD-1473 in inflammatory intestinal diseases, with the two companies sharing profits in the US and expenses related to a potential Phase 3 program.

About Gut-Selective 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, myelofibrosis, and ulcerative colitis. However, these products are known to have side effects associated with their 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

a gut-selective treatment specifically designed to distribute adequately and predominantly to the tissues of the intestinal tract, treating inflammation in those tissues while minimizing its systemic exposure. Theravance Biopharma is focused on utilizing targeted JAK inhibitors for potential treatment of a range of inflammatory intestinal diseases including ulcerative colitis and Crohn's disease, which affect roughly 900,000 and 700,000 patients in the United States, respectively.

About Theravance Biopharma

Theravance Biopharma, Inc. ("Theravance Biopharma") is a diversified biopharmaceutical company primarily focused on the discovery, development and commercialization of organ-selective medicines. Our purpose is to create transformational medicines to improve the lives of patients suffering from serious illnesses. Our research is focused in the areas of inflammation and immunology.

In pursuit of our purpose, we apply insights and innovation at each stage of our business and utilize our internal capabilities and those of partners around the world. We apply organ-selective expertise to biologically compelling targets to discover and develop medicines designed to treat underserved localized diseases and to limit systemic exposure, in order to maximize patient benefit and minimize risk. These efforts leverage years of experience in developing lung-selective medicines to treat respiratory disease, including FDA-approved YUPELRI™ (revefenacin) inhalation solution indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD). Our pipeline of internally discovered programs is targeted to address significant patient needs.

We have an economic interest in potential future payments from Glaxo Group or one of its affiliates (GSK) pursuant to its agreements with Innoviva, Inc. relating to certain programs, including TRELEGY ELLIPTA.

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, 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 (including the data therefrom), the potential characteristics, benefits and mechanisms of action of the Company's product and product candidates, and the Company's expectations for product candidates through development and potential regulatory approval and commercialization (including their potential as components of combination therapies and their differentiation from other products or potential products). 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, enrolling 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), risks that product candidates do not obtain approval from regulatory authorities, the feasibility of undertaking future clinical trials for our product candidates based on policies and feedback from regulatory authorities, 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, manufacture and commercialize products, 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'sForm 10-Q filed with the Securities and Exchange Commission (SEC) on May 10, 2019and 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:

[1] 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 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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