# Theravance Biopharma Reports Positive Results from Phase 1 Clinical Trial of TD-8236, an Investigational, Lung-Selective, Inhaled Pan-Janus Kinase (JAK) Inhibitor for Inflammatory Lung Diseases

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**Evidence of Biological Activity in the Lung with Minimal Systemic Exposure**
**Generally Well-Tolerated as a Single Dose in Healthy Volunteers and as a Once-daily Dose for Seven Days in Asthmatics**

DUBLIN, Sept. 9, 2019 /PRNewswire/ -- Theravance Biopharma, Inc. (NASDAQ: TBPH) ("Theravance Biopharma" or the "Company") today announced initial results, including positive biomarker responses, from its Phase 1 single-ascending dose (SAD) and multiple-ascending dose (MAD) clinical trial of TD-8236, an investigational, lung-selective inhaled pan-Janus kinase (JAK) inhibitor for inflammatory lung diseases. TD-8236 is specifically designed to be delivered to the lung via dry powder inhalation, targeting airway inflammation in the lung with minimal systemic exposure.

Data from the study demonstrated TD-8236 to be generally well tolerated as a single dose (up to 4500 mcg) in healthy subjects and as a once-daily dose (up to 4000 mcg) given for seven consecutive days in patients with mild asthma. There was no evidence of local irritation or bronchoconstriction. There were no severe or serious adverse events reported and no subject discontinued due to adverse events. The majority of adverse events (AEs) were deemed to be mild and all AEs resolved by follow-up visits. None of the AEs were considered related to TD-8236 and there were no clinically relevant changes seen in any safety laboratory measures including hematologic parameters, or in electrocardiograms or vital sign assessments.

The trial also quantified the amount of TD-8236 that entered the systemic circulation following inhaled administration. These pharmacokinetic results showed that plasma levels of TD-8236 in study subjects were several orders of magnitude below the levels predicted to cause systemic pharmacological activity, which is consistent with data from preclinical studies and the organ-selective design of the compound.

An additional objective of the Phase 1 program was to determine biological evidence of an anti-inflammatory effect in the lungs of asthma patients. Evidence of the biological activity of TD-8236 in the lung was demonstrated in the repeat dose portion of the study, which recruited patients with mild asthma who had elevated levels of fractional exhaled nitric oxide (FeNO). FeNO is an established disease activity biomarker in asthma, and reductions in FeNO are associated with a decrease in airway inflammation. Over the seven days of TD-8236 administration once daily by inhalation, patients experienced reductions in both pre-dose and six-hour post-dose FeNO compared to placebo at all doses above 150mcg. Importantly, this included >10pbb reduction in pre-dose FeNO on Day 7 for all doses above 150mcg.

"The results of this first-in-human study of TD-8236 are encouraging as they demonstrate promising outcomes in the areas of safety and tolerability, pharmacokinetics and preliminary pharmacodynamic activity," said Dave Singh, M.D., professor of respiratory pharmacology at the University of Manchester, UK and principal investigator of the Phase 1 study. "The minimal systemic exposure of TD-8236 observed in the study provides support for the therapy's novel, organ-selective design, while the reductions in FeNO seen in asthma patients suggest that the drug produced the desired biological activity in the target patient population. I look forward to monitoring the progress of this potential new therapy in view of the unmet treatment needs of patients with moderate to severe asthma."

"There is significant need for new therapies capable of preventing exacerbations and reducing symptoms in asthma patients whose disease remains poorly controlled on inhaled corticosteroids despite being treatment compliant. While those patients with poorly controlled disease who have the Th2-high phenotype of asthma can move on to systemic biological agents, those treatments carry the risk of systemic side effects. Additionally, those with Th2-low asthma do not benefit from biologics and many lack a therapeutic option altogether," said Brett Haumann, MD, chief medical officer of Theravance Biopharma. "We believe that TD-8236 has the potential to serve as the first inhaled nonsteroidal anti-inflammatory for the treatment of patients with more severe asthma regardless of whether their disease is characterized as Th2-high or Th2-low. We look forward to continuing to advance this exciting development program."

"TD-8236 builds upon our experience with YUPELRI in chronic obstructive pulmonary disease and TD-1473 in inflammatory intestinal diseases. TD-8236 represents our latest internally discovered development candidate to demonstrate evidence of organ selectivity," said Rick E Winningham, chief executive officer of Theravance Biopharma. "We believe our organ-selective approach to treating organ-specific disease can provide the benefit of a greater therapeutic index for patients with the promise of enhanced efficacy with less safety concerns than traditional systemic medicines. Each of our organ-selective medicines are designed specifically for the target organ system. Last week, we announced TD-5202, a gut-selective irreversible JAK3 inhibitor for inflammatory intestinal diseases progressed into clinical development. We are pleased with the progress of our pipeline programs and we look forward to sharing additional data from these programs, as well as introducing additional organ-selective programs into the clinic, over the next 12 to 18 months."

Based on these positive study results, Theravance Biopharma has initiated a Part C extension portion of the Phase 1 trial that is designed to assess a range of additional biomarkers in patients with more severe asthma to further evaluate the potential impact of TD-8236 in the patient population most

likely to benefit from this therapy. The Company also intends to initiate a lung allergen challenge Phase 2 study to provide key additional insights that will inform future clinical trials of the compound.

***About the Phase 1 Study***

The Phase 1 clinical trial of TD-8236 is a randomized, double-blind, placebo-controlled, three-part study evaluating single ascending doses (50, 150, 500, 1,500 and 4,500 mcg) in healthy subjects (Part A, completed) and multiple ascending doses (150, 500, 1,500 and 4,000 mcg QD for seven days) in patients with mild asthma (Part B, completed), as well as a third extension phase assessing lung and systemic biomarkers in moderate to severe asthma patients following seven days of dosing (Part C, ongoing). The study is designed to enroll up to a total of 124 subjects (inclusive of optional cohorts) and to investigate the safety and tolerability, pharmacokinetics and pharmacodynamics of TD-8236 via dry powder inhalation.

***About TD-8236 and Organ-Selective Pan-Janus (JAK) Kinase Inhibition***

Theravance Biopharma is focused on utilizing organ-selective JAK inhibitors for potential treatment of a range of inflammatory lung diseases, including asthma. 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. While orally-administered JAK inhibitors are currently approved for the treatment of a range of inflammatory diseases, no inhaled JAK inhibitor is approved for the treatment of airway disease, including asthma.

TD-8236 is an internally-discovered, lung-selective inhaled pan-JAK inhibitor that has demonstrated a high affinity for each of the JAK family of enzymes. The pan-JAK activity of TD-8236 suggests that it may impact a broad range of cytokines that have been associated both Th2-high and Th2-low asthma. Many moderate to severe asthma patients comprising these phenotypes remain symptomatic with currently available therapies. Importantly, TD-8236 is designed to distribute adequately and predominantly within the lungs following dry powder inhalation, with the potential to treat inflammation within that organ while minimizing systemic exposure.

***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 current dispute with Innoviva and TRC LLC, 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, the potential that the Company's research programs will progress product candidates into the clinic, the Company's expectations for product candidates through development, potential regulatory approval and commercialization (including their differentiation from other products or potential products), product sales or profit share revenue and the Company's expectations for its 2019 operating loss, excluding share-based compensation. 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: the nature of the current dispute with Innoviva and TRC LLC, the uncertainty of arbitration and litigation and the possibility that an arbitration award or litigation result involving the current dispute could be adverse to the Company, delays or difficulties in commencing, enrolling or completing clinical studies, the potential that results from clinical or non-clinical studies indicate the Company's compounds or product candidates are unsafe or ineffective, 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's Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 5, 2019 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.*

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