Theravance Biopharma, Inc. Announces Top-Line Results From Phase 2 Study of Nezulcitinib In Patients Hospitalized With Acute Lung Injury Due to COVID-19

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- Randomized, double-blind, placebo-controlled study did not meet the primary endpoint: number of Respiratory Failure-Free Days (RFDs) from randomization through Day 28 in the intent-to-treat (ITT) population
- Nezulcitinib demonstrated a favorable trend in improvement when compared to placebo for 28-day all-cause mortality rate (p=0.08)
- In a post-hoc analysis, there was an improvement in mortality (p=0.009) and time to recovery (p=0.02) in patients treated with nezulcitinib who had baseline C-reactive protein (CRP) levels <150 mg/L
- Nezulcitinib was well-tolerated when administered once-daily for up to seven days

DUBLIN and SOUTH SAN FRANCISCO, Calif., June 21, 2021 /PRNewswire/ -- Theravance Biopharma, Inc. ("Theravance Biopharma" or the "Company") (NASDAQ: TBPH), a diversified biopharmaceutical company primarily focused on the discovery, development, and commercialization of organ-selective medicines, today announced top-line results from its Phase 2 study of 3 mg once-daily nezulcitinib compared to placebo, each in combination with standard of care. Nezulcitinib is an investigational, inhaled, lung-selective, pan-Janus kinase (JAK) inhibitor in development for hospitalized patients with confirmed COVID-19 associated acute lung injury and impaired oxygenation.

"Since learning of the extensive respiratory complications in severe COVID-19, we have worked to advance the science behind inhaled lung-selective JAK inhibitors in critical diseases like COVID-19," said Rick E Winningham, Chief Executive Officer, Theravance Biopharma. "Even though this Phase 2 study, enrolling more than 200 patients, did not meet the primary endpoint, we are encouraged by the trend in the pre-specified analysis of the 28-day mortality rate in the intent-to-treat population. We are grateful to the patients and their families, our research partners, the clinical investigators, and our team at Theravance Biopharma for their important contributions."

"This is the first investigation of an inhaled JAK inhibitor in COVID-19 patients. The classification of a COVID-ALI endotype using a blood biomarker, such as C-reactive protein, may advance the understanding and stratification of a subpopulation of patients with immune characteristics that best responds to a targeted-therapeutic such as nezulcitinib," said John Belperio, MD, professor of medicine in the pulmonary and critical care department at the David Geffen School of Medicine at UCLA and trial investigator.

The study was a 1:1 randomized, double-blind, placebo-controlled, multi-center Phase 2 trial for the treatment of hospitalized COVID-19 patients (n=210) with impaired oxygenation (NCT04402866). Key endpoints were measured through Day 28. Standard of care in the study included approximately 99% receiving steroids (91% received dexamethasone).

Key Study Findings

- Outcomes:
  - Primary: No statistically significant difference in RFDs from randomization through Day 28 between nezulcitinib and placebo in ITT (median: 21 vs. 21 days; p=0.61).
  - Secondary: No difference in change from baseline at Day 7 in SaO_2/FiO_2 ratio, proportion of patients in each category of the 8-point Clinical Status scale, and proportion of patients alive and respiratory failure-free at Day 28.
  - Nezulcitinib demonstrated a favorable trend in improvement when compared to placebo for 28-day all-cause mortality (total number of deaths: 6 vs. 13, HR: 0.42, p=0.08) and time to recovery (median: 10 vs. 11 days, HR: 1.27, p=0.12).
  - In a post-hoc analysis of patients with baseline CRP (n=201):
    - In patients with CRP <150 mg/L (n=171), there was an improvement in those treated with nezulcitinib when compared to placebo in:
      - 28-day all-cause mortality (total number of deaths: 1 vs 9, HR: 0.097, p=0.009).
      - time to recovery (median: 10 vs. 11 days, HR: 1.48, p=0.02).
    - In patients with CRP $\geq$150 mg/L (n=30), there was no difference in time to recovery or 28-day all-cause mortality between those treated with nezulcitinib or placebo.
- Safety:
  - Nezulcitinib was well-tolerated; adverse events and serious adverse events occurred in 34.0% and 9.7% of patients treated with nezulcitinib, and 41.2% and 15.7% of patients treated with placebo, respectively.

    - Adverse events of liver abnormalities or disease occurred in 9.7% and 7.8% of patients treated with nezulcitinib and placebo, respectively.
    - Serious infections and venous thromboembolism occurred in 1.0% and none of the patients treated with nezulcitinib, and 2.0% and 4.9% in patients treated with placebo, respectively.
- Plasma exposure of nezulcitinib was low and consistent with expectations for a lung-selective medicine.

The Company will share these results with FDA and other regulatory agencies to seek input on protocols to further study nezulcitinib in acute hyperinflammation in the lung. A more detailed analysis of the data, including further pharmacokinetic and biomarker results, will be available in the future.

Conference Call and Live Webcast Today at 8 am ET

Theravance Biopharma will hold a conference call and live webcast accompanied by slides today at 8 am ET / 5 am PT / 1 pm IST. To participate, please dial (855) 296-9648 from the U.S. or (920) 663-6266 for international callers, using the confirmation code 6984147. Those interested in listening to the conference call live via the internet may do so by visiting Theravance.com, under the Investors section, Events and Presentations.

A replay will be available on Theravance.com for 30 days through July 21, 2021. An audio replay will also be available through 11:00 am ET on June 28, 2021, by dialing (855) 859-2056 from the U.S., or (404) 537-3406 for international callers, and then entering confirmation code 6984147.

About Nezulcitinib

Nezulcitinib, also known as TD-0903, is an investigational, inhaled, lung-selective, pan-JAK inhibitor that was discovered and developed at Theravance Biopharma. Nezulcitinib has been shown in experimental murine models to have potent, broad inhibition of JAK-STAT signaling in the airways following challenges with multiple cytokines. The organ selectivity of nezulcitinib is demonstrated preclinically via a high lung: plasma ratio and rapid metabolic clearance resulting in low systemic exposure. As an inhaled JAK inhibitor, nezulcitinib is expected to intervene broadly to interrupt excessive immune activation in the airways. Nezulcitinib, delivered via nebulization, may present a novel therapeutic modality to address the cytokine release syndrome that has been associated with acute lung injury, ventilator use, and increased morbidity and mortality in COVID-19 patients.

The Company previously reported results from the initial dose-finding portion of this Phase 2 study, in which nezulcitinib was generally well-tolerated and showed numerical improvements in clinical outcome, duration of hospital stay, and fewer deaths compared to placebo. Results of this dose-finding portion of the Phase 2 study informed a decision to progress the 3 mg dose into the larger Phase 2 study reported herein. Read more about the dose-finding portion of the Phase 2 study here.

Nezulcitinib may also provide a potential treatment for other causes of acute hyperinflammation of the lung and the prevention or delay of lung transplant rejection.

About Theravance Biopharma

Theravance Biopharma, Inc. is a diversified biopharmaceutical company primarily focused on the discovery, development and commercialization of organ-selective medicines. Its purpose is to pioneer a new generation of small molecule drugs designed to better meet patient needs. Its research is focused in the areas of inflammation and immunology.

In pursuit of its purpose, Theravance Biopharma applies insights and innovation at each stage of its business and utilizes its internal capabilities and those of partners around the world. The Company applies organ-selective expertise to target disease biologically, to discover and develop medicines that may expand the therapeutic index with the goal of maximizing efficacy and limiting systemic side effects. 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). Its pipeline of internally discovered programs is targeted to address significant patient needs.

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

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

Forward-Looking Statements

This press release contains and the conference call will contain 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 goals, designs, 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, the Company's expectations regarding its allocation of resources, 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 expenses, excluding share-based compensation and other financial results. 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 the conference call 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: disagreements with Innoviva, Inc. and TRC LLC, the uncertainty of arbitration and litigation and the possibility that the results of these proceedings could be adverse to the Company, additional future analysis of the data resulting from our clinical trial(s), 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. In addition, while we expect the effects of COVID-19 to continue to adversely impact our business operations and financial results, the extent of the impact on our ability to generate revenue from YUPELRI® (revefenacin), our clinical development programs (including but not limited to our later stage clinical programs for izencitinib and ampreloxetine), and the value of and market for our ordinary shares, will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time. These potential future developments include, but are not limited to, the ultimate duration of the COVID-19 pandemic, travel restrictions, quarantines, social distancing and business closure requirements in the United States and in other countries, other measures taken by us and those we work with to help protect individuals from contracting COVID-19, and the effectiveness of actions taken globally to contain and treat the disease, including vaccine availability, distribution, acceptance and effectiveness. Other risks affecting Theravance Biopharma are in the Company's Form 10-Q filed with the SEC on May 6, 2021 and other periodic reports filed 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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