Upstream Bio Announces First Patient Dosed in Phase 2 Clinical Trial of Verekitug in Chronic Obstructive Pulmonary Disease (COPD)

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– Global Phase 2 clinical trial, VENTURE, to evaluate the efficacy and safety of verekitug administered every 12 or 24 weeks in moderate-to-severe COPD –

– Broadens global development program for verekitug into third indication, strengthening pipeline across severe respiratory diseases including chronic rhinosinusitis with nasal polyps (CRSwNP), severe asthma, and COPD –

– Program updates also include completion of enrollment in Phase 2 clinical trial in severe asthma; top-line data now expected in first quarter of 2026 –

WALTHAM, Mass., July 08, 2025 (GLOBE NEWSWIRE) -- Upstream Bio, Inc. (Nasdaq: UPB), a clinical-stage company developing treatments for inflammatory diseases, with an initial focus on severe respiratory disorders, today announced that the first patient has been dosed in the Company's Phase 2 clinical trial evaluating verekitug in patients with COPD, broadening the global development program for verekitug into a third indication.

Verekitug is a novel antibody antagonist of the Thymic Stromal Lymphopoietin (TSLP) receptor, a key driver of the inflammatory response in allergic and inflammatory diseases such as asthma, where agents targeting TSLP have demonstrated clinical benefits.

"We are excited to expand our clinical program for verekitug into COPD with the initiation of this clinical trial," said Aaron Deykin, MD, Chief Medical Officer and head of research & development at Upstream Bio. "There are emerging data indicating that TSLP plays an important role in driving the pathobiology of COPD and the exacerbations that many patients with this disease experience. Given the results observed in our preclinical and early clinical studies in asthma, we believe that as the only known biologic in development targeting the TSLP receptor, verekitug may have the potential to advance COPD treatment with less frequent dosing and differentiated efficacy as compared to currently approved biologic therapies for this condition. This trial reflects our broader strategy to develop verekitug across multiple respiratory diseases."

VENTURE (NCT06981078) is a randomized, double-blind, placebo-controlled trial designed to assess the efficacy and safety of verekitug in approximately 670 adults with moderate-to-severe COPD. Participants will be randomized to receive verekitug at doses of 100 mg once every 12 weeks, 400 mg once every 24 weeks, or placebo, over treatment periods of between 60 weeks and up to 108 weeks.

The primary endpoint of the study is the annualized rate of moderate or severe COPD exacerbations. Secondary endpoints include changes in participants' day-to-day symptoms as well as measures of lung function, such as forced expiratory volume in one second (FEV_1). Upstream Bio has designed this trial using endpoints that, pending interactions with regulatory authorities, could produce data to support submissions for product approval. The trial is enrolling patients regardless of blood eosinophil count, with the primary analysis focusing on those with elevated eosinophils at screening. Patients without elevated eosinophils at screening will be included to facilitate exploratory analyses of verekitug's efficacy in this population.

This COPD trial is part of the broader development program for verekitug that includes separate ongoing Phase 2 studies in CRSwNP and severe asthma. Upstream Bio completed enrollment in the Phase 2 trials in CRSwNP in January 2025 and in severe asthma in June 2025 and expects top-line data readouts in the third quarter of 2025 and the first quarter of 2026, respectively.

For more information on the VENTURE Phase 2 clinical trial in COPD, visit the study listing at ClinicalTrials.gov.

About TSLP and TSLPR Blockade
Thymic Stromal Lymphopoietin (TSLP) is a cytokine that is a key driver of the inflammatory response in major allergic and inflammatory diseases, such as asthma, where disruption of TSLP signaling has been clinically validated as an effective therapeutic strategy.

TSLP activation is one of the first events in the inflammatory cascade stimulated by allergens, viruses and other triggers, initiating the activation of downstream targets such as IL-4, IL-5, IL-13, IL-17 and IgE.

Because TSLP is a target upstream in the inflammatory cascade, blocking the TSLP receptor (TSLPR) presents an opportunity for a single treatment to impact the drivers of multiple pathological inflammatory processes across a broad set of diseases.

About Verekitug
Verekitug is a novel recombinant fully human immunoglobulin G1 (IgG1) monoclonal antibody that binds to the TSLP receptor and

inhibits proinflammatory signaling initiated by TSLP. It is the only known monoclonal antibody currently in clinical development that targets and inhibits the TSLP receptor. Verekitug is currently being evaluated in three separate global, placebo-controlled, randomized Phase 2 clinical trials: the VIBRANT trial (NCT06164704) in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), the VALIANT trial (NCT06196879) in patients with severe asthma, and the VENTURE trial (NCT06981078) in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). Additionally, in May 2025, Upstream Bio initiated the VALOUR trial (NCT06966479), a long-term extension study in certain adult patients with severe asthma who completed the VALIANT Phase 2 clinical trial.

In preclinical studies, verekitug demonstrated high occupancy of the TSLP receptor and potent inhibition of TSLP signaling. Additionally, verekitug inhibited cytokine production from both CD4+ T cells and ILC2 cells and completely suppressed skin allergic reactions in a non-human primate model, suggesting that it may be effective against multiple types of inflammation.

Three clinical trials have been completed for verekitug, including a Phase 1 single-ascending dose (SAD) clinical trial and a Phase 1b multiple-ascending dose (MAD) clinical trial. In these trials, verekitug was well tolerated, had no clinically meaningful immunogenicity, and showed a predictable and consistent pharmacokinetic profile and high subcutaneous bioavailability. In patients with asthma, verekitug led to >50% reductions in fractional exhaled nitric oxide (FeNO) and blood eosinophils that were rapid and sustained for up to 24 weeks after the last dose in the Phase 1b MAD trial.

About COPD
COPD is a chronic inflammatory disease of the airways, associated with airflow worsening and episodic exacerbations that drive morbidity and mortality. Chronic inflammation causes structural changes within the lungs, narrowing already small airways and damaging lung tissue, which causes air sacs to lose functionality.

With COPD, everyday activities may result in shortness of breath and frequent exacerbations, which can result in hospitalization and drive health care utilization. People with COPD are also more likely to acquire lung infections like bronchitis and pneumonia.

COPD is the fourth leading cause of death worldwide, causing approximately 3.5 million deaths in 2021. Almost 14.2 million Americans in 2021, or 6.5% of the adult population, reported in one study that they had been diagnosed with COPD; however, the true prevalence is estimated to be higher. The prevalence and burden of COPD are projected to increase over the coming decades due to a combination of continued exposure to COPD risk factors and aging of the world's population.

Published research has shown that IL-4, IL-5, and IL-13, cytokines in the type 2 inflammation pathway, may play a role in COPD pathogenesis. Elevated levels of TSLP have been found in the airways of people with COPD, and TSLP receptor expression was highest in patients with severe COPD compared to healthy controls. Environmental triggers can also increase TSLP expression in epithelial cells, suggesting a potential role of TSLP in COPD exacerbations.

Currently available treatments for COPD include inhaled steroids to reduce airway inflammation and bronchodilator inhalers to improve airflow. Oxygen and surgery may also be used for some patients with severe COPD. Similar to asthma and CRSwNP, biologics are emerging as new and potentially transformative treatments.

About Upstream Bio
Upstream Bio is a clinical-stage biotechnology company developing treatments for inflammatory diseases, with an initial focus on severe respiratory disorders. The Company is developing verekitug, the only known antagonist currently in clinical development that targets the receptor for thymic stromal lymphopoietin (TSLP), a cytokine which is a clinically validated driver of inflammatory response positioned upstream of multiple signaling cascades that affect a variety of immune mediated diseases. The Company has advanced this highly potent monoclonal antibody into separate Phase 2 trials for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP), severe asthma, and chronic obstructive pulmonary disease (COPD). Upstream Bio's team is committed to maximizing verekitug's unique attributes to address the substantial unmet needs for patients underserved by today's standard of care. To learn more, please visit www.upstreambio.com.

Forward-Looking Statements
This press release contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, each as amended. These statements may be identified by words such as "aims," "anticipates," "believes," "continue," "could," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "predict," "project," "seeks," "should," "target," "will" and variations of these words or similar expressions. Any statements in this press release that are not statements of historical fact may be deemed to be forward-looking statements. These forward-looking statements include, without limitation, express or implied statements regarding: the global development of verekitug for the treatment of severe asthma, CRSwNP and COPD, including the initiation, timing, progress and results of ongoing and planned clinical trials; expectations for future discussions with regulatory authorities and the potential of the endpoints of the Company's clinical trials to produce data that could support submissions for product approval; expectations for the size and growth potential of the market for verekitug in COPD and the Company's ability to serve that market; and expectations regarding the differentiation, safety, efficacy, tolerability, and extended dosing interval of verekitug. Any forward-looking statements in this press release are based on the Company's current expectations, estimates and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. Readers are cautioned that actual results, levels of activity, safety, efficacy, performance or events and circumstances could differ materially from those expressed or implied in the Company's forward-looking statements due to a variety of risks and uncertainties, which include, without limitation, risks and uncertainties related to: Upstream Bio's ability to advance verekitug through clinical development, and to obtain regulatory approval of and ultimately

commercialize verekitug on the expected timeline, if at all; the initiation, timing, progress and results of clinical trials; Upstream Bio's ability to fund its development activities and achieve development goals; Upstream Bio's dependence on third parties to conduct clinical trials and manufacture verekitug, and commercialize verekitug, if approved; Upstream Bio's ability to attract, hire and retain key personnel, and protect its intellectual property; Upstream Bio's financial condition and need for substantial additional funds in order to complete development activities and commercialize verekitug, if approved; regulatory developments and approval processes of the U.S. Food and Drug Administration and comparable foreign regulatory authorities; Upstream Bio's competitors and industry; and other risks and uncertainties described in greater detail under the caption "Risk Factors" in Upstream Bio's most recent Annual Report on Form 10-K and Quarterly Report on Form 10-Q, as well as any subsequent filings with the SEC. Any forward-looking statements represent Upstream Bio's views only as of today and should not be relied upon as representing its views as of any subsequent date. Upstream Bio explicitly disclaims any obligation or undertaking to update any forward-looking statements contained herein to reflect any change in its expectations or any changes in events, conditions or circumstances on which any such statement is based except to the extent required by law, and claims the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995.

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