New England Journal of Medicine Publishes Positive Results from Phase 2 WILLOW Study of Brensocatib in Patients with Non-Cystic Fibrosis Bronchiectasis

--New Data from WILLOW Study also Presented During Late-Breaking Session at European Respiratory Society International Congress--
--Insmed to Initiate Phase 3 Program for Brensocatib in Bronchiectasis by End of 2020--

BRIDGEWATER, N.J., Sept. 7, 2020 /PRNewswire/ -- Insmed Incorporated (Nasdaq:INSM), a global biopharmaceutical company on a mission to transform the lives of patients with serious and rare diseases, today announced that final results from the Phase 2 WILLOW study of brensocatib in patients with non-cystic fibrosis bronchiectasis (NCFBE) were published online in the *New England Journal of Medicine* (NEJM). New data from subgroup analyses of the WILLOW study also were presented today during a late-breaking clinical trials session at the virtual European Respiratory Society (ERS) International Congress 2020. Brensocatib is a novel, first-in-class, oral, reversible inhibitor of dipeptidyl peptidase 1 (DPP1) being developed by Insmed for the treatment of bronchiectasis and other inflammatory diseases.

"We are very pleased that NEJM has recognized the significance of the Phase 2 WILLOW data for patients with NCFBE. These results demonstrate the potential clinical benefits of directly reducing neutrophil-mediated inflammation in bronchiectasis—a critical finding for patients who currently suffer from severe outcomes in the absence of an approved therapy," said Martina Flammer, M.D., MBA, Chief Medical Officer of Insmed. "We eagerly anticipate initiating our Phase 3 program for brensocatib in bronchiectasis later this year as we work to bring this urgently needed solution to patients."

The results published today showed that brensocatib significantly prolonged time to first pulmonary exacerbation, the primary endpoint, over the 24-week treatment period for both treatment doses versus placebo (p=0.03 for the 10 mg group; p=0.04 for the 25 mg group). The risk of exacerbation at any time during the trial was reduced by 42% for the 10 mg group versus placebo (HR 0.58, p=0.03) and by 38% for the 25 mg group versus placebo (HR 0.62, p=0.046).

Treatment with brensocatib also reduced the rate of pulmonary exacerbations, a key secondary endpoint. Patients treated with brensocatib experienced a 36% reduction in the 10 mg arm (p=0.04) and a 25% reduction in the 25 mg arm (p=0.17), compared with the placebo arm. In addition, mean concentrations of active neutrophil elastase (NE) in sputum showed dose-dependent reductions compared with placebo over the 24-week treatment period.

Importantly, study results were consistent among subgroups based on age, baseline NE concentrations, prior exacerbation history, bronchiectasis severity index, and lung function.

"The WILLOW study demonstrated that among patients with NCFBE who have a history of frequent exacerbations, treatment with brensocatib significantly prolonged the time to first exacerbation and reduced the risk of exacerbation over the treatment period. Annualized rates of exacerbation were also lower compared to placebo," said lead author James Chalmers, MBChB, Ph.D., Professor and Consultant Respiratory Physician at the School of Medicine, University of Dundee, UK. "These results are critically important given the lack of approved pharmaceutical therapies to reduce the risk of exacerbation—the major driver of morbidity and mortality in patients with bronchiectasis. The results also validate the novel mechanism of action of brensocatib and highlight the potential benefits of reducing neutrophil serine protease activity."

In addition to the results published in NEJM, new data from the WILLOW study were presented today at the ERS International Congress. Subgroup analyses showed that brensocatib consistently prolonged time to first exacerbation and reduced rates of exacerbation among patient subgroups analyzed by baseline disease severity, *P. aeruginosa* infection, and sputum NE concentration. Further, brensocatib reduced the sputum concentrations of all three neutrophil serine proteases (NSPs) assessed (NE, proteinase 3, and cathepsin G).

Brensocatib was generally well-tolerated in the WILLOW study. Rates of adverse events (AEs) leading to drug discontinuation in patients treated with placebo, brensocatib 10 mg, and brensocatib 25 mg were 11%, 7%, and 7%, respectively. The most common AEs in patients treated with brensocatib were cough, headache, sputum increase, dyspnea, infective exacerbation of bronchiectasis, and diarrhea.

Rates of adverse events of special interest (AESIs) in patients treated with placebo, brensocatib 10 mg, and brensocatib 25 mg,

respectively, were as follows: rates of skin events (including hyperkeratosis) were 12%, 15%, and 24%; rates of dental events were 4%, 16%, and 10%; and rates of infections considered AESIs were 18%, 14%, and 17%. Hyperkeratosis was reported in 1/85, 3/81, and 1/89 patients treated with placebo, brensocatib 10 mg, and brensocatib 25 mg, respectively. The study included extensive dental evaluations to closely monitor progression of periodontal disease. The results did not raise a signal about dental safety. The percentage of patients with change in periodontal pocket depth ≥2 mm and absolute value of ≥5 mm (the threshold of concern for periodontal disease) were 12%, 11%, and 12% for placebo, brensocatib 10 mg, and brensocatib 25 mg, respectively. No skin or dental adverse events were considered serious.

Brensocatib received breakthrough therapy designation from the U.S. Food and Drug Administration inJune 2020 for the treatment of adult patients with NCFBE for reducing exacerbations. Insmed plans to initiate a Phase 3 program for brensocatib in bronchiectasis by the end of 2020.

About WILLOW

WILLOW was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, multi-national, Phase 2 study to assess the efficacy, safety and tolerability, and pharmacokinetics of brensocatib administered once daily for 24 weeks in patients with non-cystic fibrosis bronchiectasis (NCFBE). WILLOW was conducted at 116 sites and enrolled 256 adult patients diagnosed with NCFBE who had at least two documented pulmonary exacerbations in the 12 months prior to screening. Patients were randomized 1:1:1 to receive either 10 mg or 25 mg of brensocatib or matching placebo. The primary efficacy endpoint was the time to first pulmonary exacerbation over the 24-week treatment period in the brensocatib arms compared to the placebo arm.

About Brensocatib

Brensocatib is a small molecule, oral, reversible inhibitor of dipeptidyl peptidase I (DPP1) being developed by Insmed for the treatment of patients with bronchiectasis. DPP1 is an enzyme responsible for activating neutrophil serine proteases (NSPs), such as neutrophil elastase, in neutrophils when they are formed in the bone marrow. Neutrophils are the most common type of white blood cell and play an essential role in pathogen destruction and inflammatory mediation. In chronic inflammatory lung diseases, neutrophils accumulate in the airways and result in excessive active NSPs that cause lung destruction and inflammation. Brensocatib may decrease the damaging effects of inflammatory diseases such as bronchiectasis by inhibiting DPP1 and its activation of NSPs.

About Non-Cystic Fibrosis Bronchiectasis

Non-cystic fibrosis bronchiectasis (NCFBE) is a severe, chronic pulmonary disorder in which the bronchi become permanently dilated due to a cycle of infection, inflammation, and lung tissue damage. The condition is marked by frequent pulmonary exacerbations requiring antibiotic therapy and/or hospitalizations. Symptoms include chronic cough, excessive sputum production, shortness of breath, and repeated respiratory infections, which can worsen the underlying condition. NCFBE affects approximately 340,000 to 520,000 patients in the U.S. Today, there are no approved therapies specifically targeting NCFBE in the U.S., Europe, or Japan.

About Insmed

Insmed Incorporated is a global biopharmaceutical company on a mission to transform the lives of patients with serious and rare diseases. Insmed's first commercial product, ARIKAYCE® (amikacin liposome inhalation suspension), is the first and only therapy approved in the United States for the treatment of refractory *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen for adult patients with limited or no alternative treatment options. MAC lung disease is a chronic, debilitating condition that can cause severe and permanent lung damage. Insmed is also advancing brensocatib, a novel oral reversible inhibitor of dipeptidyl peptidase 1 with therapeutic potential in bronchiectasis and other inflammatory diseases, and treprostinil palmitil, an inhaled formulation of a treprostinil prodrug that may offer a differentiated product profile for rare pulmonary disorders, including pulmonary arterial hypertension. For more information, visit www.insmed.com.

Forward-looking Statements

This press release contains forward-looking statements that involve substantial risks and uncertainties. "Forward-looking statements," as that term is defined in the Private Securities Litigation Reform Act of 1995, are statements that are not historical facts and involve a number of risks and uncertainties. Words herein such as "may," "will," "should," "could," "would," "expects," "plans," "anticipates," "believes," "estimates," "projects," "predicts," "intends," "potential," "continues," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) may identify forward-looking statements.

The forward-looking statements in this press release are based upon the Company's current expectations and beliefs, and involve known and unknown risks, uncertainties and other factors, which may cause the Company's actual results, performance and achievements and the timing of certain events to differ materially from the results, performance, achievements or timing discussed, projected, anticipated or indicated in any forward-looking statements. Such risks, uncertainties and other factors include, among others, the following: the risk that brensocatib does not prove effective or safe for patients in future clinical

studies, including the STOP-COVID19 study; business or economic disruptions due to catastrophes or other events, including natural disasters or public health crises; impact of the novel coronavirus (COVID-19) pandemic and efforts to reduce its spread on our business, employees, including key personnel, patients, partners and suppliers; failure to successfully commercialize or maintain U.S. approval for ARIKAYCE, the Company's only approved product; uncertainties in the degree of market acceptance of ARIKAYCE by physicians, patients, third-party payors and others in the healthcare community; the Company's inability to obtain full approval of ARIKAYCE from the FDA, including the risk that the Company will not timely and successfully complete the study to validate a PRO tool and complete the confirmatory post-marketing study required for full approval of ARIKAYCE; inability of the Company, PARI or the Company's other third party manufacturers to comply with regulatory requirements related to ARIKAYCE or the Lamira® Nebulizer System; the Company's inability to obtain adequate reimbursement from government or third-party payors for ARIKAYCE or acceptable prices for ARIKAYCE; development of unexpected safety or efficacy concerns related to ARIKAYCE or brensocatib; inaccuracies in the Company's estimates of the size of the potential markets for ARIKAYCE or brensocatib or in data the Company has used to identify physicians; expected rates of patient uptake, duration of expected treatment, or expected patient adherence or discontinuation rates; the Company's inability to create an effective direct sales and marketing infrastructure or to partner with third parties that offer such an infrastructure for distribution of ARIKAYCE; failure to obtain regulatory approval to expand ARIKAYCE's indication to a broader patient population; failure to successfully conduct future clinical trials for ARIKAYCE, brensocatib and the Company's other product candidates, including due to the Company's limited experience in conducting preclinical development activities and clinical trials necessary for regulatory approval and the Company's inability to enroll or retain sufficient patients to conduct and complete the trials or generate data necessary for regulatory approval; risks that the Company's clinical studies will be delayed or that serious side effects will be identified during drug development; failure to obtain, or delays in obtaining, regulatory approvals for ARIKAYCE outside the U.S. or for the Company's product candidates in the U.S., Europe, Japan or other markets, including theUnited Kingdom as a result of its recent exit from the European Union; failure of third parties on which the Company is dependent to manufacture sufficient quantities of ARIKAYCE or the Company's product candidates for commercial or clinical needs, to conduct the Company's clinical trials, or to comply with laws and regulations that impact the Company's business or agreements with the Company; the Company's inability to attract and retain key personnel or to effectively manage the Company's growth; the Company's inability to adapt to its highly competitive and changing environment; the Company's inability to adequately protect its intellectual property rights or prevent disclosure of its trade secrets and other proprietary information and costs associated with litigation or other proceedings related to such matters; restrictions or other obligations imposed on the Company by its agreements related to ARIKAYCE or the Company's product candidates, including its license agreements with PARI and AstraZeneca AB, and failure of the Company to comply with its obligations under such agreements; the cost and potential reputational damage resulting from litigation to which the Company is or may become a party, including product liability claims; the Company's limited experience operating internationally; changes in laws and regulations applicable to the Company's business, including any pricing reform, and failure to comply with such laws and regulations; inability to repay the Company's existing indebtedness and uncertainties with respect to the Company's ability to access future capital; and delays in the execution of plans to build out an additional FDA-approved third-party manufacturing facility and unexpected expenses associated with those plans.

The Company may not actually achieve the results, plans, intentions or expectations indicated by the Company's forward-looking statements because, by their nature, forward-looking statements involve risks and uncertainties because they relate to events and depend on circumstances that may or may not occur in the future. For additional information about the risks and uncertainties that may affect the Company's business, please see the factors discussed in Item 1A, "Risk Factors," in the Company's Annual Report on Form 10-K for the year ended December 31, 2019, our Quarterly Report on Form 10-Q for the quarter ended March 31, 2020 and any subsequent Company filings with the SEC.

The Company cautions readers not to place undue reliance on any such forward-looking statements, which speak only as of the date of this press release. The Company disclaims any obligation, except as specifically required by law and the rules of the SEC, to publicly update or revise any such statements to reflect any change in expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

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