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# Insmmed Initiates Frontline Clinical Trial Program for ARIKAYCE® (amikacin liposome inhalation suspension) in Patients with MAC Lung Disease

**--First Patient Dosed in Post-Marketing Program Intended to Support Full FDA Approval of ARIKAYCE and sNDA in Newly Diagnosed Patients--**

**--Program Includes ARISE and ENCORE: Two Inter-Related Studies Conducted in Parallel--**

BRIDGEWATER, N.J., Jan. 4, 2021 /PRNewswire/ -- Insmmed Incorporated (Nasdaq: INSM), a global biopharmaceutical company on a mission to transform the lives of patients with serious and rare diseases, today announced that the first patient was dosed in late December, 2020, in the frontline clinical trial program of ARIKAYCE® (amikacin liposome inhalation suspension) in patients with nontuberculous mycobacterial (NTM) lung disease caused by *Mycobacterium avium* complex (MAC). The program consists of ARISE, an interventional study designed to validate cross-sectional and longitudinal characteristics of patient-reported outcome (PRO) tools in MAC lung disease, and ENCORE, a pivotal trial designed to establish, using the PRO tools validated in the ARISE trial, the clinical benefits and evaluate the safety of ARIKAYCE in patients with newly diagnosed MAC lung disease.

ARIKAYCE was granted accelerated approval by the U.S. Food and Drug Administration (FDA) in September of 2018 for the treatment of MAC lung disease as part of a combination antibacterial drug regimen for adult patients who have limited or no alternative treatment options. It is the first and only therapy approved in the U.S. for the treatment of MAC lung disease. The frontline clinical trial program is intended to fulfill the FDA's post-marketing requirement to allow for full approval of ARIKAYCE in the U.S. and to support a supplemental new drug application (sNDA) for the use of ARIKAYCE as a frontline treatment for patients with MAC lung disease.

"We are very pleased to initiate the frontline clinical development program for ARIKAYCE, potentially laying the groundwork for a new standard of care for patients with MAC lung disease," said Martina Flammer, M.D., MBA, Chief Medical Officer of Insmmed. "ARIKAYCE has already changed the treatment landscape of refractory MAC lung disease since its FDA approval more than two years ago, and we are excited to build on that foundation with the initiation of these studies. Our hope is that this program will not only provide pivotal data for ARIKAYCE in a frontline setting, but also will validate PRO tools for the assessment of treatment benefit in clinical trials of patients with MAC lung disease going forward."

ARISE is a randomized, double-blind, placebo-controlled Phase3b study in adult patients with newly diagnosed MAC lung disease that aims to generate evidence demonstrating the domain specification, reliability, validity, and responsiveness of PRO-based scores. Patients will be randomized 1:1 to receive ARIKAYCE plus background regimen or placebo plus background regimen once daily for six months. Patients will then discontinue all study treatments and remain in the trial for one month for the continued assessment of PRO endpoints. The study is expected to enroll approximately 100 patients.

ENCORE is a randomized, double-blind, placebo-controlled phase3b study to evaluate the efficacy and safety of an ARIKAYCE-based regimen in patients with newly diagnosed MAC lung disease. Patients will be randomized 1:1 to receive ARIKAYCE plus background regimen or placebo plus background regimen once daily for 12 months. Patients will then discontinue all study treatments and remain in the trial for three months for the assessment of durability of culture conversion. The primary endpoint is change from Baseline to Month 13 in respiratory symptom score. The key secondary endpoint is the proportion of subjects achieving durable culture conversion at Month 15. ENCORE is expected to enroll approximately 250 patients.

Approximately 150 sites are expected to be initiated globally for the ARISE and ENCORE clinical trials.

More information on these studies is available at [clinicaltrials.gov](https://clinicaltrials.gov) (ARISE: NCT04677543; ENCORE: NCT04677569).

## About ARIKAYCE

ARIKAYCE is approved in the United States as ARIKAYCE® (amikacin liposome inhalation suspension) and in the EU as ARIKAYCE® Liposomal 590 mg Nebuliser Dispersion. Current international treatment guidelines recommend the use of ARIKAYCE for appropriate patients. ARIKAYCE is a novel, inhaled, once-daily formulation of amikacin, an established antibiotic

that was historically administered intravenously and associated with severe toxicity to hearing, balance, and kidney function. Insmed's proprietary PULMOVANCE® liposomal technology enables the delivery of amikacin directly to the lungs, where liposomal amikacin is taken up by lung macrophages where the infection resides, while limiting systemic exposure. ARIKAYCE is administered once daily using the Lamira® Nebulizer System manufactured by PARI Pharma GmbH (PARI).

### **About PARI Pharma and the Lamira® Nebulizer System**

ARIKAYCE is delivered by a novel inhalation device, the Lamira® Nebulizer System, developed by PARI. Lamira® is a quiet, portable nebulizer that enables efficient aerosolization of ARIKAYCE via a vibrating, perforated membrane. Based on PARI's 100-year history working with aerosols, PARI is dedicated to advancing inhalation therapies by developing innovative delivery platforms and new pharmaceutical formulations that work together to improve patient care.

### **IMPORTANT SAFETY INFORMATION FOR ARIKAYCE IN THE U.S.**

#### **WARNING: RISK OF INCREASED RESPIRATORY ADVERSE REACTIONS**

**ARIKAYCE has been associated with an increased risk of respiratory adverse reactions, including hypersensitivity pneumonitis, hemoptysis, bronchospasm, and exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases.**

**Hypersensitivity Pneumonitis** has been reported with the use of ARIKAYCE in the clinical trials. Hypersensitivity pneumonitis (reported as allergic alveolitis, pneumonitis, interstitial lung disease, allergic reaction to ARIKAYCE) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (3.1%) compared to patients treated with a background regimen alone (0%). Most patients with hypersensitivity pneumonitis discontinued treatment with ARIKAYCE and received treatment with corticosteroids. If hypersensitivity pneumonitis occurs, discontinue ARIKAYCE and manage patients as medically appropriate.

**Hemoptysis** has been reported with the use of ARIKAYCE in the clinical trials. Hemoptysis was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (17.9%) compared to patients treated with a background regimen alone (12.5%). If hemoptysis occurs, manage patients as medically appropriate.

**Bronchospasm** has been reported with the use of ARIKAYCE in the clinical trials. Bronchospasm (reported as asthma, bronchial hyperreactivity, bronchospasm, dyspnea, dyspnea exertional, prolonged expiration, throat tightness, wheezing) was reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (28.7%) compared to patients treated with a background regimen alone (10.7%). If bronchospasm occurs during the use of ARIKAYCE, treat patients as medically appropriate.

**Exacerbations of underlying pulmonary disease** has been reported with the use of ARIKAYCE in the clinical trials. Exacerbations of underlying pulmonary disease (reported as chronic obstructive pulmonary disease (COPD), infective exacerbation of COPD, infective exacerbation of bronchiectasis) have been reported at a higher frequency in patients treated with ARIKAYCE plus background regimen (14.8%) compared to patients treated with background regimen alone (9.8%). If exacerbations of underlying pulmonary disease occur during the use of ARIKAYCE, treat patients as medically appropriate.

**Anaphylaxis and Hypersensitivity Reactions:** Serious and potentially life-threatening hypersensitivity reactions, including anaphylaxis, have been reported in patients taking ARIKAYCE. Signs and symptoms include acute onset of skin and mucosal tissue hypersensitivity reactions (hives, itching, flushing, swollen lips/tongue/uvula), respiratory difficulty (shortness of breath, wheezing, stridor, cough), gastrointestinal symptoms (nausea, vomiting, diarrhea, crampy abdominal pain), and cardiovascular signs and symptoms of anaphylaxis (tachycardia, low blood pressure, syncope, incontinence, dizziness). Before therapy with ARIKAYCE is instituted, evaluate for previous hypersensitivity reactions to aminoglycosides. If anaphylaxis or a hypersensitivity reaction occurs, discontinue ARIKAYCE and institute appropriate supportive measures.

**Ototoxicity** has been reported with the use of ARIKAYCE in the clinical trials. Ototoxicity (including deafness, dizziness, presyncope, tinnitus, and vertigo) were reported with a higher frequency in patients treated with ARIKAYCE plus background regimen (17%) compared to patients treated with background regimen alone (9.8%). This was primarily driven by tinnitus (7.6% in ARIKAYCE plus background regimen vs 0.9% in the background regimen alone arm) and dizziness (6.3% in ARIKAYCE plus background regimen vs 2.7% in the background regimen alone arm). Closely monitor patients with known or suspected auditory or vestibular dysfunction during treatment with ARIKAYCE. If ototoxicity occurs, manage patients as medically appropriate, including potentially discontinuing ARIKAYCE.

**Nephrotoxicity** was observed during the clinical trials of ARIKAYCE in patients with MAC lung disease but not at a higher frequency than background regimen alone. Nephrotoxicity has been associated with the aminoglycosides. Close monitoring of patients with known or suspected renal dysfunction may be needed when prescribing ARIKAYCE.

**Neuromuscular Blockade:** Patients with neuromuscular disorders were not enrolled in ARIKAYCE clinical trials. Patients with known or suspected neuromuscular disorders, such as myasthenia gravis, should be closely monitored since aminoglycosides may aggravate muscle weakness by blocking the release of acetylcholine at neuromuscular junctions.

**Embryo-Fetal Toxicity:** Aminoglycosides can cause fetal harm when administered to a pregnant woman. Aminoglycosides, including ARIKAYCE, may be associated with total, irreversible, bilateral congenital deafness in pediatric patients exposed *in utero*. Patients who use ARIKAYCE during pregnancy, or become pregnant while taking ARIKAYCE should be apprised of the potential hazard to the fetus.

**Contraindications:** ARIKAYCE is contraindicated in patients with known hypersensitivity to any aminoglycoside.

**Most Common Adverse Reactions:** The most common adverse reactions in Trial 1 at an incidence  $\geq 5\%$  for patients using ARIKAYCE plus background regimen compared to patients treated with background regimen alone were dysphonia (47% vs 1%), cough (39% vs 17%), bronchospasm (29% vs 11%), hemoptysis (18% vs 13%), ototoxicity (17% vs 10%), upper airway irritation (17% vs 2%), musculoskeletal pain (17% vs 8%), fatigue and asthenia (16% vs 10%), exacerbation of underlying pulmonary disease (15% vs 10%), diarrhea (13% vs 5%), nausea (12% vs 4%), pneumonia (10% vs 8%), headache (10% vs 5%), pyrexia (7% vs 5%), vomiting (7% vs 4%), rash (6% vs 2%), decreased weight (6% vs 1%), change in sputum (5% vs 1%), and chest discomfort (5% vs 3%).

**Drug Interactions:** Avoid concomitant use of ARIKAYCE with medications associated with neurotoxicity, nephrotoxicity, and ototoxicity. Some diuretics can enhance aminoglycoside toxicity by altering aminoglycoside concentrations in serum and tissue. Avoid concomitant use of ARIKAYCE with ethacrynic acid, furosemide, urea, or intravenous mannitol.

**Overdosage:** Adverse reactions specifically associated with overdose of ARIKAYCE have not been identified. Acute toxicity should be treated with immediate withdrawal of ARIKAYCE, and baseline tests of renal function should be undertaken. Hemodialysis may be helpful in removing amikacin from the body. In all cases of suspected overdosage, physicians should contact the Regional Poison Control Center for information about effective treatment.

## U.S. INDICATION

LIMITED POPULATION: ARIKAYCE<sup>®</sup> is indicated in adults, who have limited or no alternative treatment options, for the treatment of *Mycobacterium avium* complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. As only limited clinical safety and effectiveness data for ARIKAYCE are currently available, reserve ARIKAYCE for use in adults who have limited or no alternative treatment options. This drug is indicated for use in a limited and specific population of patients.

**This indication is approved under accelerated approval based on achieving sputum culture conversion (defined as 3 consecutive negative monthly sputum cultures) by Month 6. Clinical benefit has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.**

**Limitation of Use:** ARIKAYCE has only been studied in patients with refractory MAC lung disease defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of ARIKAYCE is not recommended for patients with non-refractory MAC lung disease.

Patients are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch), or call 1-800-FDA-1088. You can also call the Company at 1-844-4-INSMED.

Please see [Full Prescribing Information](#).

## About Insmmed

Insmmed Incorporated is a global biopharmaceutical company on a mission to transform the lives of patients with serious and rare diseases. Insmmed's first commercial product is a first-in-disease therapy approved in the United States and the European Union to treat a chronic, debilitating lung disease. The Company is also progressing a robust pipeline of investigational therapies targeting areas of serious unmet need, including neutrophil-mediated inflammatory diseases and rare pulmonary disorders. Insmmed is headquartered in Bridgewater, New Jersey, with a growing footprint across Europe and in Japan. For more information, visit [www.insmed.com](http://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: failure to obtain, or delays in obtaining, regulatory approvals for ARIKAYCE outside the U.S. or European Union or for the Company's product candidates in the U.S., Europe, Japan or other markets, including the United Kingdom as a result of the United Kingdom's exit from the European Union; failure to successfully commercialize ARIKAYCE, the Company's only approved product, in the United States or European Union (amikacin liposome inhalation suspension and Liposomal 590 mg Nebuliser Dispersion, respectively), or to maintain U.S. or EU approval for ARIKAYCE; 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 the Company's business, employees, including key personnel, patients, partners and suppliers; the risk that brensocaticib does not prove to be effective or safe for patients in ongoing and future clinical studies, including the ASPEN and STOP-COVID19 studies; 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 the confirmatory post-marketing clinical trial 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<sup>®</sup> 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 the Company's product candidates; inaccuracies in the Company's estimates of the size of the potential markets for ARIKAYCE or its product candidates 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 or any of the Company's product candidates that are approved in the future; failure to obtain regulatory approval to expand ARIKAYCE's indication to a broader patient population; failure to successfully conduct future clinical trials for ARIKAYCE, brensocaticib, treprostinil palmitil inhalation powder (TPIP) and the Company's other product candidates due to the Company's limited experience in conducting preclinical development activities and clinical trials necessary for regulatory approval and its potential inability to enroll or retain sufficient patients to conduct and complete the trials or generate data necessary for regulatory approval, among other things; risks that the Company's clinical studies will be delayed or that serious side effects will be identified during drug development; 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 the Company's agreements or 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 third-party manufacturing facility approved by the appropriate regulatory authorities 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, the Company's Quarterly Reports on Form 10-Q for the quarters ended March 31, 2020, June 30, 2020 and September 30, 2020, and any subsequent Company filings with the Securities and Exchange Commission (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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