INSMED ANNOUNCES POSITIVE TOPLINE RESULTS FROM PHASE 3 ARISE STUDY OF ARIKAYCE® (AMIKACIN LIPOSOME INHALATION SUSPENSION) IN PATIENTS WITH NTM LUNG DISEASE CAUSED BY MAC

—QOL-B Respiratory Domain Shown to Work Effectively as Patient-Reported Outcome Tool in Patients with MAC Lung Disease; to be Proposed to FDA as Primary Endpoint in ENCORE with No Modifications—

—Patients Treated with ARIKAYCE Plus Macrolide-Based Background Regimen Had Meaningfully Larger Improvements in QOL-B Respiratory Score with Strong Trend Toward Significance vs. Macrolide-Based Background Regimen Alone—

—ARIKAYCE-Treated Patients Had Nominally Statistically Significantly Higher Culture Conversion Rates at Month 7 vs. Comparator (78.8% vs. 47.1%, p=0.0010); Culture Conversion Began Earlier and Was More Likely to Persist Through Month 7 with ARIKAYCE Regimen—

—No New or Unexpected Safety Signals Observed—

—Insmed to Explore Accelerating Filing for ARIKAYCE in Newly Infected MAC Lung Disease Patients with Global Regulators on Basis of ARISE Data—

—Insmed to Host Investor Call at 8:30 a.m. ET on Tuesday, September 5—

BRIDGEWATER, N.J., Sept. 5, 2023 /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 positive topline results from its Phase 3 ARISE study of ARIKAYCE in patients with newly diagnosed or recurrent nontuberculous mycobacterial (NTM) lung infection caused by *Mycobacterium avium* complex (MAC) who had not started antibiotics.

The study met its primary objective of demonstrating that the Quality of Life – Bronchiectasis (QOL-B) respiratory domain works effectively as a patient-reported outcome (PRO) instrument in patients with MAC lung disease. Based on these results, Insmed plans to propose to the U.S. Food and Drug Administration (FDA) that the QOL-B respiratory domain PRO be the primary endpoint for the ENCORE study without any modifications.

Patients in ARISE (N=99) were randomized 1:1 to treatment with ARIKAYCE plus macrolide-based background regimen (ARIKAYCE arm) or placebo plus macrolide-based background regimen (comparator arm) for six months, followed by one month off treatment. ARIKAYCE-treated patients performed better than those in the comparator arm as measured by the QOL-B instrument, with 43.8% of patients achieving an improvement in QOL-B respiratory score above the estimated meaningful within-subject score difference of 14.8, compared with 33.3% of patients in the comparator arm. While the study was not powered to show a statistically significant difference between treatment arms, a strong trend toward significance was observed for improvement from baseline at Month 7 (12.24 vs. 7.76, p=0.1073).

Patients in the ARIKAYCE arm also achieved nominally statistically significantly higher culture conversion rates at Month 7 versus patients in the comparator arm (78.8% vs. 47.1%, p=0.0010), and culture conversion was faster and more likely to persist through Month 7 for the ARIKAYCE arm.

"The ARISE study represents a clear and unambiguous win for the entire NTM community. We are thrilled that these results not only validate a PRO tool in NTM lung disease, but also show that patients treated with an ARIKAYCE-based regimen felt better versus patients in the comparator arm, as measured by this instrument. Coupled with extraordinary culture conversion outcomes, these findings give us great confidence that our Phase 3 registrational trial, ENCORE, is well-positioned to achieve both statistically and clinically meaningful results, leading to a sizeable increase in the number of patients who could hope to benefit from ARIKAYCE," said Martina Flammer, M.D., MBA, Chief Medical Officer of Insmed.

Based on the results of ARISE, Insmed plans to explore with global regulators accelerating the filing for approval of ARIKAYCE in newly infected patients with MAC lung disease. In parallel, the Company continues to enroll patients in ENCORE, which will use the PRO tool that has been validated in ARISE, with 250 patients expected to be enrolled by the end of 2023. Enrollment in ENCORE is expected to continue into 2024 to ensure a high degree of statistical powering and Insmed anticipates reporting topline data from ENCORE in 2025.

"I want to thank the many patients, caregivers, and investigators who participated in ARISE and made this impressive outcome possible. We look forward to discussing these excellent results from this well-executed study in the near future with regulators," noted Kevin Mange, M.D., M.S.C.E., Chief Development Officer of Insmed.

Additional ARISE Study Findings

Insmed reported the following additional results from the ARISE study:

Culture Conversion
Consistent with prior clinical studies, a higher proportion of patients in the ARIKAYCE arm achieved culture conversion by Month 6 (defined as negative cultures at Months 5 and 6) compared to patients in the comparator arm (80.6% vs. 63.9%, p=0.0712). Among patients who achieved culture conversion by Month 6, more patients in the ARIKAYCE arm achieved the first of their two required monthly negative cultures for clinical conversion at Month 1 versus the comparator arm (74.3% vs. 46.7%). As reported above, at Month 7 (one month following the cessation of treatment), 47.1% of patients in the comparator arm were culture-converted vs. 78.8% of patients in the ARIKAYCE arm, suggesting that ARIKAYCE-treated patients are more likely to remain negative.

Correlation Between Culture Conversion and QOL-B Performance
Patients in the ARIKAYCE arm who achieved culture conversion at both Month 6 and Month 7 had nominally statistically significantly greater improvements in QOL-B respiratory domain scores at Month 7 compared to patients in the ARIKAYCE arm who did not achieve culture conversion (15.74 vs. 3.53, p=0.0167 at Month 6 and 14.89 vs. 4.50, p=0.0416 at Month 7).

PROMIS Fatigue-Short Form 7a
The Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue-Short Form 7a was also assessed in the study. While both treatment arms showed improvements in the PROMIS Fatigue scores from Baseline to Month 7, the difference between treatment groups was not significant, with 35.5% of ARIKAYCE patients achieving a within-subject meaningful difference of at least a 4-unit decrease (a negative change signifies improvement) compared to 29.4% of subjects in the comparator arm. As previously noted, the study was not powered to show a statistically significant difference between treatment arms.

Safety and Tolerability
The discontinuation rate of ARIKAYCE or the placebo used in the comparator arm was 22.9% in the ARIKAYCE arm and 7.8% in the comparator arm. Study completion rates were 91.7% in the ARIKAYCE arm and 94.1% in the comparator arm. No new safety events were observed in the ARIKAYCE arm, and the safety profile in general was as expected in both treatment arms. Treatment-emergent adverse events (TEAEs) were reported by 91.7% of patients in the ARIKAYCE arm and 80.4% of patients in the comparator arm. The most common TEAEs were dysphonia (41.7% for the ARIKAYCE arm vs. 3.9% for the comparator arm), cough (27.1% vs. 7.8%), diarrhea (27.1% vs. 25.5%), and COVID-19 (12.5% vs. 9.8%). Of the treatment-emergent serious adverse events observed in the trial, none were determined to be related to ARIKAYCE by investigators and none were deemed related to COVID-19.

About the ARISE & ENCORE Clinical Trial Program

ARIKAYCE was granted accelerated approval by the 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 ARISE and ENCORE 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 for the use of ARIKAYCE as a treatment for patients with a MAC lung infection.

ARISE was a global, randomized, double-blind, placebo-controlled, Phase 3b study in adult patients with newly diagnosed or recurrent MAC lung disease who had not started antibiotics that aimed to generate evidence demonstrating the domain specification, reliability, validity, and responsiveness of PRO-based scores. Patients were randomized 1:1 to receive ARIKAYCE plus background regimen or placebo plus background regimen once daily for six months. Patients then discontinued all study treatments and remained in the trial for one month for the continued assessment of PRO endpoints. The study enrolled 99 patients.

The ongoing ENCORE trial is a randomized, double-blind, placebo-controlled, Phase 3b study to evaluate the efficacy and safety of an ARIKAYCE-based regimen in patients with newly diagnosed or recurrent MAC lung disease who have not started antibiotics. Patients are 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 patients achieving durable culture conversion at Month 15.

About the Validation of PRO Tools in MAC Lung Disease

Today, there are no established clinical endpoints to evaluate the benefits of treatment in patients with MAC lung disease. The QOL-B instrument is a self-administered PRO questionnaire used to assess symptoms, functioning, and health-related quality of life in adults with non-cystic fibrosis bronchiectasis. Insmed's clinical trial program to establish that the Respiratory Symptom Domain of the QOL-B is reliable for measuring respiratory symptoms in patients with MAC lung disease generated evidence to support content validity based on concept elicitation and cognitive interviews with patients, and generated evidence to support measurement properties based on cross-sectional analyses using screening and baseline blinded data from both ARISE and a subset of patients from ENCORE (first 131 patients enrolled). Longitudinal analyses were based on ARISE data. Researchers used the Patient Global Impression of Severity (PGI-S) questionnaire, a simple, one-question categorical rating of symptom severity, as an anchor to estimate a range of meaningful within-subject score differences. The PROMIS Fatigue Short Form 7a was also evaluated in this clinical trial program using an identical approach.

Conference Call
Insmed management will host a conference call for investors beginning at 8:30 a.m. ET on Tuesday, September 5, 2023, to discuss the ARISE results. Shareholders and other interested parties may participate in the conference call by dialing (888) 210-2654 (U.S. and international) and referencing access code 7862189. The call will also be webcast live on the Company's website at www.insmed.com.

A replay of the conference call will be accessible approximately one hour after its completion through October 5, 2023, by dialing (800) 770-2030 (U.S. and international) and referencing access code 7862189. A webcast of the call will also be archived for 90 days under the Investor Relations section of the Company's website at www.insmed.com.

About MAC Lung Disease
Mycobacterium avium complex (MAC) lung disease is a rare and serious disorder that can significantly increase morbidity and mortality. Patients with MAC lung disease can experience a range of symptoms that often worsen over time, including chronic cough, dyspnea, fatigue, fever, weight loss, and chest pain. In some cases, MAC lung disease can cause severe, even permanent damage to the lungs, and can be fatal. MAC lung disease is an emerging public health concern worldwide with significant unmet need.

About ARIKAYCE
ARIKAYCE is approved in the United States as ARIKAYCE® (amikacin liposome inhalation suspension), in Europe as ARIKAYCE® Liposomal 590 mg Nebuliser Dispersion, and in Japan as ARIKAYCE® inhalation 590 mg (amikacin sulfate inhalation drug product). 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 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 ≥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® 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, or call 1–800–FDA–1088. You can also call the Company at 1-844-4-INSMED.

Please see Full Prescribing Information.

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 is a first-in-disease therapy approved in the United States, Europe, and Japan to treat a chronic, debilitating lung disease. The Company is progressing a robust pipeline of investigational therapies targeting areas of serious unmet need, including neutrophil-mediated inflammatory diseases and rare pulmonary disorders. Insmed is also advancing an early-stage research engine encompassing a wide range of technologies and modalities, including artificial intelligence-driven protein engineering, gene therapy, and protein manufacturing. Insmed is headquartered in Bridgewater, New Jersey, with additional offices and research locations throughout the United States, Europe, and Japan. Visit www.insmed.com to learn more.

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 timings 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., Europe or Japan; failure to successfully commercialize ARIKAYCE, the Company's only approved product, in the U.S., Europe or Japan (amikacin liposome inhalation suspension, Liposomal 590 mg Nebuliser Dispersion, and amikacin sulfate inhalation drug product, respectively), or to maintain U.S., European or Japanese approval for ARIKAYCE; business or economic disruptions due to catastrophes or other events, including natural disasters or public health crises; 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 successfully or in a timely manner complete 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® 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; failure to obtain regulatory approval to expand ARIKAYCE's indication to a broader patient population; failure to successfully conduct future clinical trials for ARIKAYCE 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; and failure of third parties on which the Company is dependent to manufacture sufficient quantities of ARIKAYCE 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 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, 2022 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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