NEWS RELEASE

Merck Initiates Phase 3 Study Evaluating Ohtuvayre® (ensifentrine) for the Prevention of COPD Exacerbations in Adult Patients Receiving Standard of Care With a History of Exacerbations

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ENHANCE-3 study represents Merck's commitment to addressing the burden of COPD exacerbations

OHTUVAYRE® is the first and only novel inhaled mechanism for the maintenance treatment of COPD in more than 20 years to combine bronchodilation and non-corticosteroid anti-inflammatory effects

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced the initiation of ENHANCE-3 (**NCT07874815**), a Phase 3 randomized clinical trial evaluating OHTUVAYRE (ensifentrine) for the prevention of chronic obstructive pulmonary disease (COPD) exacerbations in adult patients receiving standard of care (SOC) with a history of exacerbations. Recruitment of the ENHANCE-3 trial has begun, and the first patients are now enrolling in the United States.

"Many patients with COPD continue to experience persistent symptoms such as shortness of breath, despite current standard-of-care therapy. For these patients, exacerbations remain a major driver of disease progression and diminished quality of life," said Dr. Mahesh Patel, vice president, global clinical development, Merck Research Laboratories. "The initiation of the Phase 3 ENHANCE-3 study marks an important step in our efforts to further strengthen the body of evidence supporting OHTUVAYRE and its potential to address significant unmet needs in COPD care. We remain committed to advancing innovative research to help the millions of people impacted by this

disease worldwide."

The ENHANCE-3 Phase 3 trial plans to enroll approximately 2,136 patients in 28 countries across the world. The primary endpoint of the study is the annualized rate of adjudicated moderate or severe COPD exacerbations, and secondary endpoints include lung function, health-related quality of life, severe exacerbations and safety. We look forward to sharing the results of the ENHANCE-3 trial with regulatory authorities globally.

Based on the **ENHANCE-1** and **ENHANCE-2** studies, OHTUVAYRE was approved by the U.S. Food and Drug Administration (FDA) in June 2024 for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients. OHTUVAYRE is the first and only novel inhaled mechanism for the maintenance treatment of COPD in more than 20 years to combine bronchodilation and non-corticosteroid anti-inflammatory effects. OHTUVAYRE is also being evaluated in a Phase 2 clinical trial for the treatment of non-cystic fibrosis bronchiectasis.

About OHTUVAYRE® (ensifentrine)

OHTUVAYRE (ensifentrine) is a first-in-class novel selective dual inhibitor of phosphodiesterase 3 and 4 (PDE3 and PDE4). It is the first and only inhaled therapy for the maintenance treatment of adults with COPD to combine bronchodilation and non-corticosteroid anti-inflammatory effects in one molecule. OHTUVAYRE has been evaluated in the Phase 3 clinical program ENHANCE ("Ensifentrine as a Novel inHAled Nebulized COPD thErapy") for COPD maintenance treatment, where it met the primary endpoint in both ENHANCE-1 and ENHANCE-2, demonstrating statistically significant and clinically meaningful improvements in lung function. OHTUVAYRE has a demonstrated safety profile that supports use as a maintenance treatment in a range of adults with COPD.

About ENHANCE-3 (NCT07874815)

ENHANCE-3 is a Phase 3, randomized, double-blind, placebo-controlled study evaluating approximately 2,136 patients with a history of at least one moderate or severe COPD exacerbation in the previous year while receiving standard of care (SOC), defined as long-acting muscarinic antagonists (LAMA), long-acting beta-agonists (LABA) and inhaled corticosteroids (ICS), or LAMA and LABA if ICS is not appropriate. Participants will be randomized 1:1 to receive OHTUVAYRE twice daily plus SOC or placebo plus SOC. The primary endpoint is the annualized rate of adjudicated moderate or severe COPD exacerbations over 52 weeks. The secondary endpoints are the change from baseline in FEV1 (forced expiratory volume in one second, a standard measure of lung function) AUC0-4h (area under the curve, 0-4 hours post-dose) at week 12, responder status on the SGRQ (St. George's Respiratory Questionnaire, a measure of health-related quality of life in COPD) at week 24, the annualized rate of adjudicated severe COPD exacerbations over 52 weeks, as well as overall safety.

Key eligibility criteria for the trial include adults 40 to 80 years of age with a confirmed diagnosis of COPD for at

least 12 months, a current or former smoking history, use of the same SOC for at least two months, and a documented history of at least one moderate or severe COPD exacerbation within the year prior to enrollment.

About chronic obstructive pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition that causes restricted airflow and breathing problems, most commonly in the form of emphysema and chronic bronchitis. Shortness of breath is one of the most common and debilitating symptoms of COPD, often limiting patients' ability to stay active and carry out everyday activities. Other symptoms include an ongoing cough, wheezing, chest tightness or heaviness and fatigue. Many patients remain persistently symptomatic despite treatment, and these symptoms can worsen into exacerbations. Smoking and air pollution are the most common causes of COPD. More than 390 million people were estimated to be suffering from COPD worldwide as of 2019. There is no cure for COPD.

OHTUVAYRE Indication and Select Safety Information

Indication

OHTUVAYRE is indicated for the maintenance treatment of chronic obstructive pulmonary disease (COPD) in adult patients.

Select safety information

Contraindications OHTUVAYRE is contraindicated in patients with hypersensitivity to ensifentrine or any component of this product.

Warnings and precautions

Acute Episodes of Bronchospasm OHTUVAYRE should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. OHTUVAYRE has not been studied in the relief of acute symptoms and extra doses of OHTUVAYRE should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting bronchodilator.

Paradoxical Bronchospasm As with other inhaled medicines, OHTUVAYRE may produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs following dosing with OHTUVAYRE, it should be treated immediately with an inhaled, short-acting bronchodilator. OHTUVAYRE should be discontinued immediately and alternative therapy should be instituted.

Psychiatric Events Including Suicidality Treatment with OHTUVAYRE is associated with an increase in psychiatric adverse reactions. Psychiatric events including suicide-related adverse reactions were reported in clinical studies in patients who received OHTUVAYRE (1 suicide attempt and 1 suicide). Additionally, the most commonly reported psychiatric adverse reactions in the pooled 24-week safety population were insomnia (6 patients [0.6%] OHTUVAYRE 3 mg; 2 patients [0.3%] placebo), and anxiety (2 patients [0.2%] OHTUVAYRE 3 mg; 1 patient [0.2%] placebo). Depression-related reactions including depression, major depression, and adjustment disorder with depressed mood occurred in 4 patients (0.4%) receiving OHTUVAYRE and no patients receiving placebo.

Before initiating treatment with OHTUVAYRE, healthcare providers should carefully weigh the risk and benefits of treatment with OHTUVAYRE in patients with a history of depression and/or suicidal thoughts or behavior. Patients, their caregivers, and families should be advised of the need to be alert for the emergence or worsening of insomnia, anxiety, depression, suicidal thoughts, or other mood changes, and if such changes occur to contact their healthcare provider. Healthcare providers should carefully evaluate the risks and benefits of continuing treatment with OHTUVAYRE if such events occur.

Adverse reactions The most common adverse reactions ≥1% in OHTUVAYRE and greater than placebo in the pooled population in the ENHANCE-1 and ENHANCE-2 clinical trials were back pain (1.8% vs 1.0%), hypertension (1.7% vs 0.9%), urinary tract infection (1.3% vs 1.0%), and diarrhea (1.0% vs 0.7%).

These are not all of the possible risks associated with OHTUVAYRE.

Dosage and administration The recommended dosage of OHTUVAYRE is 3 mg (one unit-dose ampule) twice daily, once in the morning and once in the evening, administered by oral inhalation using a standard jet nebulizer with a mouthpiece.

Special populations

Pediatric Use The safety and effectiveness of OHTUVAYRE have not been established in pediatric patients.

Lactation There are no data on the presence of ensifentrine in human milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OHTUVAYRE and any potential adverse effects on the breastfed child from OHTUVAYRE or from the underlying maternal condition.

Geriatric Use In clinical trials, patients aged 65 and older showed no overall differences in the safety or effectiveness of OHTUVAYRE compared with younger adults, but greater sensitivity in some older individuals cannot

be ruled out.

Hepatic Impairment Ensifentrine systemic exposure increased by 2.3-fold in subjects with moderate or severe hepatic impairment compared with healthy subjects. Use OHTUVAYRE with caution in patients with hepatic impairment.

Before prescribing OHTUVAYRE® (ensifentrine), please read the accompanying **Prescribing Information**. The **Patient Information** and **Instructions for Use** also are available.

Merck's focus on cardiometabolic and respiratory diseases

Merck has a long history of developing treatments for cardiometabolic and respiratory diseases. Building on a legacy that began nearly 70 years ago with the introduction of our first cardiovascular therapy, we are committed to advancing research for patients impacted by cardiometabolic and respiratory diseases. Our focus spans a range of diseases, including atherosclerotic cardiovascular disease, heart failure, pulmonary hypertension and chronic obstructive pulmonary disease (COPD).

Advancements in the treatment of cardiometabolic and respiratory diseases can make a critical difference for patients and health systems around the world. At Merck, we strive for scientific excellence and innovation in all stages of research, from discovery through approval and life cycle management.

About Merck

At Merck, known as MSD outside of the United States and Canada, we are unified around our purpose: We use the power of leading-edge science to save and improve lives around the world. For more than 130 years, we have brought hope to humanity through the development of important medicines and vaccines. We aspire to be the premier research-intensive biopharmaceutical company in the world – and today, we are at the forefront of research to deliver innovative health solutions that advance the prevention and treatment of diseases in people and animals. We foster a diverse and inclusive global workforce and operate responsibly every day to enable a safe, sustainable and healthy future for all people and communities. For more information, visit **www.merck.com** and connect with us on **X (formerly Twitter)**, **Facebook**, **Instagram**, **YouTube** and **LinkedIn**.

Forward-Looking statement of Merck & Co., Inc., Rahway, N.J., USA

This news release of Merck & Co., Inc., Rahway, N.J., USA (the "company") includes "forward-looking statements" within the meaning of the safe harbor provisions of the U.S. Private Securities Litigation Reform Act of 1995. These statements are based upon the current beliefs and expectations of the company's management and are subject to

significant risks and uncertainties. There can be no guarantees with respect to pipeline candidates that the candidates will receive the necessary regulatory approvals or that they will prove to be commercially successful. If underlying assumptions prove inaccurate or risks or uncertainties materialize, actual results may differ materially from those set forth in the forward-looking statements.

Risks and uncertainties include but are not limited to, general industry conditions and competition; general economic factors, including interest rate and currency exchange rate fluctuations; the impact of pharmaceutical industry regulation and health care legislation in the United States and internationally; global trends toward health care cost containment; technological advances, new products and patents attained by competitors; challenges inherent in new product development, including obtaining regulatory approval; the company's ability to accurately predict future market conditions; manufacturing difficulties or delays; financial instability of international economies and sovereign risk; dependence on the effectiveness of the company's patents and other protections for innovative products; and the exposure to litigation, including patent litigation, and/or regulatory actions.

The company undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise. Additional factors that could cause results to differ materially from those described in the forward-looking statements can be found in the company's Annual Report on Form 10-K for the year ended December 31, 2025 and the company's other filings with the Securities and Exchange Commission (SEC) available at the SEC's Internet site (**www.sec.gov**).

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