NEWS RELEASE

# Merck’s Gefapixant (45 mg Twice Daily) Significantly Decreased Cough Frequency Compared to Placebo at Week 12 and 24 in Patients with Refractory or Unexplained Chronic Cough

9/8/2020

## Data from Phase 3 COUGH-1 and COUGH-2 Trials Presented at the Virtual European Respiratory Society (ERS) International Congress 2020

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, has announced the results from two pivotal Phase 3 trials (COUGH-1 and COUGH-2) evaluating the efficacy and safety of gefapixant (MK-7264), an investigational, orally administered, selective P2X3 receptor antagonist, for the potential treatment of refractory or unexplained chronic cough. COUGH-1 and COUGH-2 are the first companion Phase 3 trials ever conducted in patients with refractory chronic cough, a cough that persists despite appropriate treatment of underlying conditions, or unexplained chronic cough, a cough where the underlying cause cannot be identified despite a thorough evaluation. In these studies, adult patients treated with gefapixant 45 mg twice daily demonstrated a statistically significant reduction in 24-hour cough frequency (measured objectively, as coughs per hour, using 24-hour sound recordings) versus placebo at 12 weeks (COUGH-1) (18.45% reduction relative to placebo, 95% CI [-32.92, -0.86; p=0.041]) and 24 weeks (COUGH-2) (14.64% reduction relative to placebo, 95% CI [-26.07, -1.43; p=0.031]). The gefapixant 15 mg twice daily treatment arms did not meet the primary efficacy endpoint in either Phase 3 study.

“It is estimated that between 5 and 10% of adults globally suffer from chronic cough. A subset of these patients have refractory or unexplained chronic cough and appear more sensitive to various triggers that do not typically

cause cough in healthy subjects. These include everyday things such as talking, laughing, a change in air temperature or exposure to aerosols or food odors, and to date treatment options are extremely limited for these patients," said Dr. Lorcan McGarvey, Clinical Professor, Wellcome-Wolfson Institute of Experimental Medicine, School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast. "Given the significant unmet need for these patients, we are strongly encouraged by the findings of COUGH-1 and COUGH-2 and the potential for a new therapeutic option for patients who are struggling with the burden of this disease, often for many years without relief."

"COUGH-1 and COUGH-2 are the first companion Phase 3 trials in refractory or unexplained chronic cough, underscoring Merck's commitment to fully researching the potential for gefapixant in this patient population," said Dr. Roy Baynes, senior vice president and head of global clinical development, chief medical officer, Merck Research Laboratories. "Both trials met the primary endpoint at the 45 mg twice daily dosage, significantly reducing cough frequency in these patients, and we are grateful for the opportunity to share these data with the scientific community."

These results were presented at the virtual European Respiratory Society (ERS) International Congress 2020 (abstract #3800). Merck plans to share data from COUGH-1 and COUGH-2 with regulatory authorities worldwide.

## Study design and additional data from COUGH-1 and COUGH-2

COUGH-1 (NCT03449134) and COUGH-2 (NCT03449147) are international Phase 3, randomized, double-blind, placebo-controlled, studies to evaluate the efficacy and safety of gefapixant in reducing cough frequency in adult participants with refractory or unexplained chronic cough. A total of 2,044 participants(75% female, mean age 58 years, mean cough duration 11 years) were treated in COUGH-1 (n=730) and COUGH-2 (n=1,314). In both studies, patients were randomized to one of three groups: gefapixant 45 mg twice daily, gefapixant 15 mg twice daily, or placebo. Participants remained on their assigned treatment at randomization throughout both studies. The primary efficacy outcomes measure for COUGH-1 and COUGH-2 were 24-hour cough frequency at Week 12, and 24-hour cough frequency at week 24, respectively, measured using an ambulatory digital audio recording device. Secondary endpoints in both trials included awake coughs per hour and percentage of participants with a greater than 1.3-point increase from baseline in the Leicester Cough Questionnaire (LCQ) total score. COUGH-1 had a 12-week treatment period and a 40-week extension period, while COUGH-2 had a 24-week treatment period and a 28-week extension period. Primary safety outcomes include the percentage of patients experiencing greater than one adverse event (AE) during treatment and follow up, and the percentage of patients discontinuing treatment because of adverse events.

In COUGH-1 and COUGH-2, treatment with gefapixant 45 mg twice daily resulted in a significant reduction in objectively measured 24-hour cough frequency in participants with refractory or unexplained chronic cough. In

these studies, on average, participants receiving gefapixant 45 mg twice daily in the COUGH-1 trial experienced a 62% reduction in cough frequency, and in the COUGH-2 trial experienced a 63% reduction in cough frequency, compared with baseline.

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| | COUGH-1 (Week 12) | | | COUGH-2 (Week 24) | | |
|---|---|---|---|---|---|---|
| | Placebo | Gefapixant 15 mg | Gefapixant 45 mg | Placebo | Gefapixant 15 mg | Gefapixant 45 mg |
| Efficacy | | | | | | |
| N included in Analysis | 222 | 227 | 217 | 419 | 415 | 409 |
| Baseline Geometric Mean 24-Hr Cough Frequency (coughs/hr) | 22.83 | 19.86 | 18.24 | 19.48 | 19.35 | 18.55 |
| Geometric Mean 24-Hr Cough Frequency at Primary Timepoint | 10.33 | 9.66 | 7.05 | 8.34 | 8.10 | 6.83 |
| Estimated Relative Reduction (%) (95% CI) vs Placebo* | -- | 1.58 (-16.12, 23.01) p=0.872 | -18.45 (-32.92, -0.86) p=0.041 | -- | -1.14 (-14.27, 14.02) p=0.875 | -14.64 (-26.07, -1.43) p=0.031 |

*Estimated relative reduction (%) vs placebo was estimated by 1OO*(exp(diff) -1), where diff was the difference provided by the analysis of the log transformed variable.

The secondary endpoints in COUGH-1 and COUGH-2 support the primary observation of the studies. Awake cough frequency results were generally similar to the 24-hour cough frequency outcome, reaching statistical significance in the 45 mg twice daily group in COUGH-2 (15.79% estimated relative reduction, 95% CI [-27.27, -2.50; p=0.022]) and trending towards significance in COUGH-1 (17.68% estimated relative reduction, 95% CI [-32.57, 0.50; p=0.056]). Significantly more participants in the gefapixant 45 mg twice daily group at week 24 demonstrated a clinically important improvement in cough-related quality of life, with an odds ratio of 1.41 (p=0.042) compared with placebo. Of the participants in the 45 mg group, 77.1% experienced a clinically important level of improvement in their quality of life related to cough, as measured using the LCQ.

The safety and tolerability profile of gefapixant was consistent with that reported in previous studies. The incidence of serious AEs was similar between treatments (<4%). Discontinuations due to AEs were more frequent in the 45 mg group (15% in COUGH-1 and 20% in COUGH-2) compared to the 15 mg (3% in COUGH-1 and 8% in COUGH-2) and placebo groups (3% and 5%, respectively). Taste-related AEs occurred at higher incidence in the 45 mg group (58.0% in COUGH-1 and 68.6% in COUGH-2) compared to the 15 mg (10.7% in COUGH-1 and 19.5% in COUGH-2) and placebo (3.3% in COUGH-1 and 8.3% in COUGH-2) groups. The majority of taste-related AEs were mild to moderate.

## About Gefapixant

Gefapixant is an investigational, orally administered, selective P2X3 receptor antagonist, for the potential treatment of refractory or unexplained chronic cough. P2X3 receptors are one of the receptor types found on sensory nerve

fibers, predominantly C fibers, in the airway lining. Chemical stimuli, including adenosine triphosphate (ATP), can be released from airway lining cells due to processes including airway inflammation, irritation, and mechanical stress/injury. Binding of extracellular ATP to P2X3 receptors on C fibers in the airway can be sensed as a signal of potential damage, creating an action potential, which may initiate coughing. Blockade of extracellular ATP binding to P2X3 receptors is thought to reduce sensory C fiber activation and subsequently, coughing.

## About Chronic Cough

The prevalence of chronic cough (a cough lasting more than 8 weeks) is estimated at 5-10% of the general adult population globally. In a subset of these cases, patients either do not respond to treatment of underlying conditions (such as asthma or gastroesophageal reflux), known as refractory chronic cough (RCC), or they have no identifiable underlying condition despite a thorough evaluation, known as unexplained chronic cough (UCC). There are currently no approved therapies for the treatment of RCC or UCC.

## About Merck

For more than 125 years, Merck, known as MSD outside of the United States and Canada, has been inventing for life, bringing forward medicines and vaccines for many of the world's most challenging diseases in pursuit of our mission to save and improve lives. We demonstrate our commitment to patients and population health by increasing access to health care through far-reaching policies, programs and partnerships. Today, Merck continues to be at the forefront of research to prevent and treat diseases that threaten people and animals – including cancer, infectious diseases such as HIV and Ebola, and emerging animal diseases – as we aspire to be the premier research-intensive biopharmaceutical company in the world. For more information, visit **www.merck.com** and connect with us on **Twitter**, **Facebook**, **Instagram**, **YouTube** and **LinkedIn**.

## Forward-Looking Statement of Merck & Co., Inc., Kenilworth, N.J., USA

This news release of Merck & Co., Inc., Kenilworth, 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 products that the products 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 the recent global

outbreak of novel coronavirus disease (COVID-19); 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 2019 Annual Report on Form 10-K 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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