have increased sensitivity for classifying voxels close to the −856 HU threshold (3). However, further investigations into the pathophysiological mechanisms associated with the PRM and DPM classification differences are needed.

This study emphasizes that the measurement of fSAD by CT is critically dependent on breathing instructions. A precise assessment of fSAD is crucial for determining early disease etiology (7) and the efficacy of treatments in patients with early stages of COPD as well as in symptomatic smokers without spirometric evidence of obstructive lung disease (8). Therapies that target fSAD have the potential not only to reduce air trapping but also to slow and even reverse the development of COPD.

It is recognized that the measurement of fSAD by CT is critically dependent on breathing instructions. Coaching to RV in a clinical setting will require careful training of CT technologists to deliver instructions similar to those delivered in a pulmonary function laboratory. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Efficacy and Safety of Gefapixant for Refractory or Unexplained Chronic Cough over 52 Weeks

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Data availability: The data-sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, is available at https://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via e-mail to dataaccess@merck.com.

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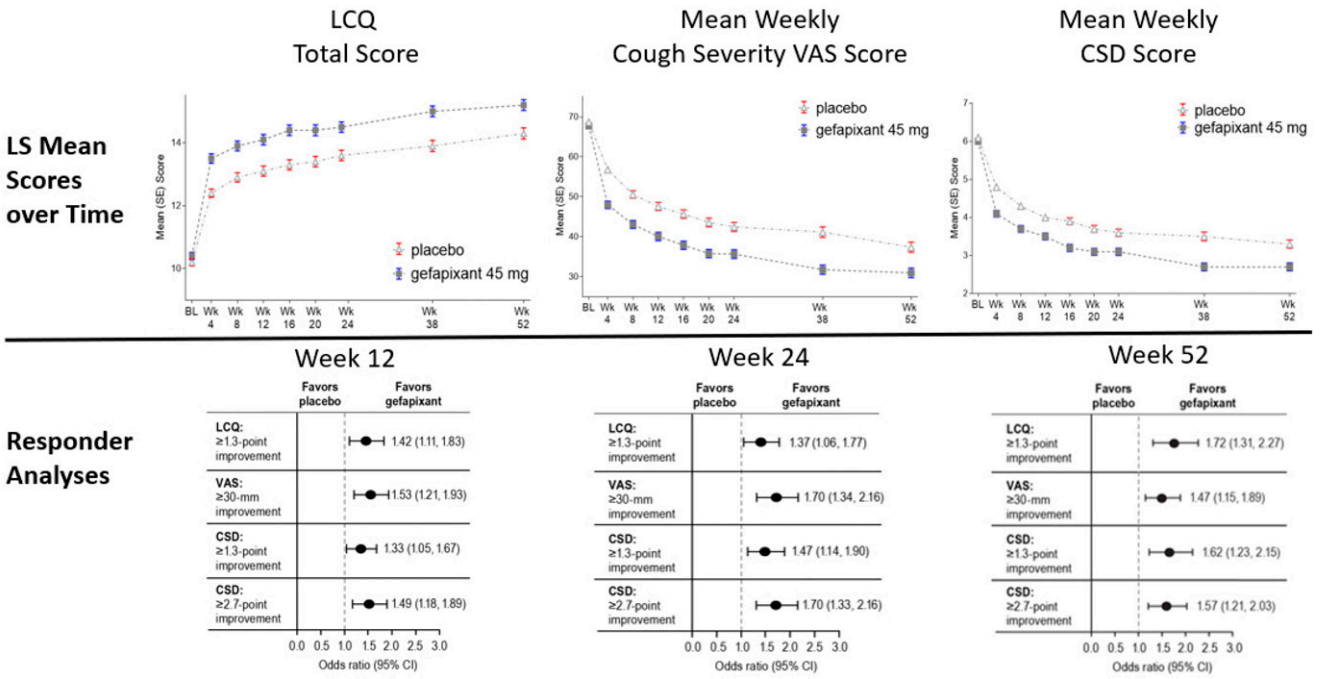

Figure 1. Mean (SE) patient-reported outcome values over 52 weeks and odds ratios at Weeks 12, 24, and 52 for achieving clinically meaningful improvements in the LCQ total score, mean weekly cough severity VAS, and mean weekly CSD for gefapixant 45 mg twice daily versus placebo. BID = twice daily; CSD = Cough Severity Diary; LCQ = Leicester Cough Questionnaire; VAS = visual analog scale.

To the Editor:

Gefapixant is a P2X3 receptor antagonist that has demonstrated efficacy in COUGH-1 [A Study of Gefapixant (MK-7264) in Adult Participants with Chronic Cough (MK-7264-027)] and COUGH-2 [A Study of Gefapixant (MK-7264) in Adult Participants with Chronic Cough (MK-7264-030)], two phase III trials for the treatment of refractory chronic cough (RCC; a cough that persists despite treatment of cough-related conditions) and unexplained chronic cough (UCC; a cough that persists despite a full clinical evaluation that does not identify a comorbid condition associated with chronic cough) (1). Data demonstrating the durability of effect on RCC and UCC are important, as is the evaluation of outcome measures that reflect the patient perspective. No prior study has explored the durability of chronic cough treatment over time periods of up to 52 weeks. We present patient-reported outcome (PRO) data evaluating long-term benefit and safety over 52 weeks from COUGH-1 and COUGH-2.

Methods

The design, entry criteria, and procedures for COUGH-1 and COUGH-2 have been described previously (1, 2). The main study periods, during which the primary efficacy endpoint of 24-hour cough frequency (measured objectively) was evaluated, were 12 weeks (COUGH-1) and 24 weeks (COUGH-2). The main study periods were followed by blinded 40-week (COUGH-1) and 28-week (COUGH-2) extension periods for a total of 52 weeks; 24-hour cough frequency was not evaluated in the extension periods.

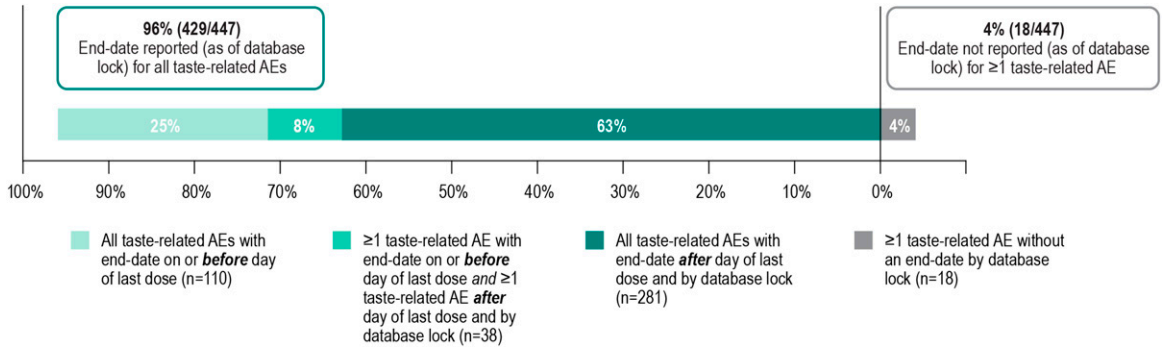

Figure 2. Resolution of taste-related AEs reported by 447 participants in the gefapixant 45 mg twice daily group. AE = adverse event.

The present analysis evaluated a pooled dataset of both studies through 52 weeks of treatment. Although gefapixant 45 mg twice daily demonstrated statistically significant improvement versus placebo in primary and secondary endpoints during the main study periods, gefapixant 15 mg twice daily did not (1); therefore, the PRO and safety and tolerability results for the gefapixant 45 mg arm and placebo arm are presented here.

PROs were collected through 52 weeks as secondary endpoints and included the Leicester Cough Questionnaire (LCQ), cough severity visual analog scale (VAS), and Cough Severity Diary (CSD). The LCQ is a 19-item questionnaire assessing cough-specific health-related quality of life; a lower score (total LCQ score range, 3–21) indicates a lower quality of life, and a ⩾1.3-point increase from baseline in the LCQ total score was considered to be a clinically meaningful improvement (3). Participants assessed cough severity on a VAS from 0 to 100 mm; a ⩾30-mm reduction was considered clinically meaningful improvement (4). The CSD includes seven items (total CSD score range, 1–10); levels of clinically meaningful improvement were assessed as a ⩾1.3-point (first threshold) or ⩾2.7-point (second threshold) reduction from baseline (5). Efficacy was evaluated with least-squares means over time and responder analyses using definitions of clinically meaningful improvement at Weeks 12, 24, and 52 (analyzed using a logistic regression model) (1).

Adverse events (AEs) were assessed at each clinical visit (screening, baseline, randomization), then every 4 weeks until Week 24, then every 7 weeks thereafter. Data on all AEs reported in the trials have been described previously (1). Among these, taste-related AEs (dysgeusia, ageusia, hypogeusia, or related terms) were prespecified for analysis (1). *Post hoc* analyses of discontinuation due to a taste-related AE, time to discontinuation due to a taste-related AE, and time to resolution of taste-related AEs were conducted.

Results

The pooled trial population included 2,044 participants across three treatment arms. Of these, 1,631 continued in the extension periods and 1,534 completed 52 weeks of treatment. Participants were mostly female (75%) and White (80%), with mean cough duration of 11.3 years (1). In this analysis, focused on two treatment arms, 683 participants were treated with gefapixant 45 mg twice daily, and 675 participants were treated with placebo.

Least-squares mean PROs in both the placebo and gefapixant groups improved over 52 weeks, with numerically greater improvement observed with gefapixant 45 mg twice daily versus placebo (Figure 1). The odds for achieving a clinically meaningful response were improved for gefapixant 45 mg twice daily versus placebo at each time point for each PRO (Figure 1).

At 52 weeks, there was a higher proportion of participants who reported at least one taste-related AE in the gefapixant 45 mg twice daily arm (447 of 683; 65.4%) than in the placebo arm (47 of 675; 7.0%). There was also a higher proportion of participants who discontinued because of a taste-related AE in the gefapixant 45 mg twice daily arm (95 of 683; 13.9%) than in the placebo arm (2 of 675; 0.3%). Of the discontinuations resulting from taste-related AEs in the gefapixant 45 mg twice daily group, half occurred during the initial 4 weeks of treatment.

As previously reported, among 447 participants with taste-related AEs in the gefapixant 45 mg twice daily group, 429 (96%) had documented resolution as of database lock (1); 63% had resolution after discontinuation, whereas 25% had resolution on or before the day of the last dose (Figure 2). There were 18 (4%) participants who did not have documented resolution as of database lock. An analysis of follow-up information obtained as of December 2021 (after database lock) showed that only 7 of 683 gefapixant participants had unresolved taste-related AEs, which was nearly identical to the number of placebo participants with unresolved taste-related AEs ($n = 6$ of 675 participants).

Discussion

The results of this analysis demonstrate that a greater proportion of participants receiving gefapixant 45 mg twice daily than those who received placebo achieved clinically meaningful improvements in PROs that were maintained over 52 weeks of treatment. In the gefapixant 45 mg twice daily arm, the most common AEs were related to taste, as seen in previous gefapixant studies (6, 7) and consistent with preclinical evidence indicating that expression of either P2X3 homotrimers or P2X2/3 heterotrimers or both on gustatory nerves is essential for taste responses in mice (6–8).

In the vast majority (99%) of participants, taste-related AEs resolved, and this percentage was the same in the gefapixant and placebo arms. Although most of these AEs resolved after the last day of treatment, one-fourth of participants had resolution while still receiving gefapixant. As previously observed, taste-related AEs were not considered serious or a cause of hospitalization, meaning that even the taste-related AEs that led to discontinuation can be considered an issue of tolerability rather than safety.

Consistent with previous trials of chronic cough treatments, and as seen with both objective cough frequency and PROs in the main study periods, a robust placebo response was observed through Week 52; this may be consistent with the identified role of the central nervous system component of the cough reflex arc (9). Nonetheless, these studies demonstrate efficacy with gefapixant and are the largest and longest prospective clinical trials in RCC or UCC to date. These data indicate that gefapixant may be an important, durable treatment for RCC and UCC, which are long-lasting conditions with a significant unmet need for safe and effective treatments. ■

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Reply to Cottin *et al.*, to Johannson *et al.*, to Scholand and Wells, and to Crowley *et al.*

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From the Authors:

We thank Cottin and colleagues, Johannson and colleagues, Scholand and Wells, and Crowley and colleagues (1–4), for their letters, published in the November 15, 2022 issue of the *Journal*, regarding our 2022 clinical practice guideline addressing both idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF), hereinafter referred to as the IPF-PPF guideline (5).

We agree with Cottin and colleagues that "[d]isease progression, at whatever rate, should lead to a reevaluation of current management, often including the institution of antifibrotic therapy" (1, p. 1294). We never intended to imply that patients who progress quickly and meet the criteria for PPF before one year need to wait the full year before being defined and managed as having PPF. In such cases, the patient has met the criteria within the past year.

We respectfully disagree with the notion that "criteria for progression should be dissociated from the timelines during which they occur" (1, p. 1294). The importance of including one year in the diagnostic criteria was to ensure that the threshold values for change in FVC and D_{LCO} are appropriate. A 5% decrease in the FVC is clinically important if it occurs over a year or less but is less likely to be clinically important if it is spread out over many years. The committee tried to be as evidence based as possible in its approach to selecting diagnostic criteria, and most studies defined changes in physiological measures over one year.

Johannson and colleagues describe two key issues related to clinical practice guideline development (2). First, how much evidence is necessary to develop a clinical practice guideline? Second, what type of content is appropriate for a clinical practice guideline?

The long-standing position of the American Thoracic Society, European Respiratory Society, and Asociación Latinoamericana de Tórax is that the need for a guideline should be based on the importance of the questions and need for guidance, not the amount or type of evidence that exists, which the Japanese Respiratory Society also accepted for this guideline as a co-sponsoring society. In theory, until the required systematic review is performed, one does not know how much evidence exists. A clinical practice guideline is defined by the approach used. Clinically important questions are asked, and then a systematic review is performed to find the best available evidence to inform the question. It is common that the systematic review fails to identify randomized trials or controlled observational evidence. In such cases, it is acceptable for guideline committees to make research recommendations or, alternatively, to use uncontrolled evidence or unsystematic clinical observations to inform clinical recommendations, as long as the poor quality of evidence is clearly acknowledged (6). Consistent with this approach, the IPF-PPF guidelines described evidence in detail, made multiple research recommendations, and provided a single clinical recommendation on the basis of very low-quality evidence (5).

Along these lines, Johannson and colleagues imply that addressing PPF in a clinical practice guideline was putting the cart before the horse; in other words, the body of evidence should have been allowed to grow before doing a guideline rather than developing a guideline during the early stages of evidence generation. We agree that more evidence would have been informative and may have yielded more clinical recommendations than research recommendations. However, the topic was deemed clinically important, with an urgent need for guidance, as the INBUILD trial had prompted an abrupt paradigm shift toward an en bloc approach