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Published in:
American Journal of Respiratory and Critical Care Medicine

Document Version:
Peer reviewed version

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

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AJRCCM Articles in Press. Published March 30, 2023 as 10.1164/rccm.202211-2128LE

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Funding: Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. This study was supported by the Northern Ireland Clinical Research Network (NICRN) and by the UK National Institute of Health Research (NIHR) Clinical Research Facilities and Clinical Research Network staff. Support was also provided by the NIHR-Wellcome King's Clinical Research Facility, NIHR Biomedical Research Centre at South London, Maudsley NHS Foundation Trust, King's College London, and NIHR Manchester Clinical Research Facility. JAS is funded by the NIHR Manchester Biomedical Research Centre and a Wellcome Investigator Award and is an NIHR senior investigator.

Author Contributions: SSB, PVD, JAS, AHM, LPM, IDP, JS, BI, SAG, and DRM contributed to the conception, design, or planning of the study. SSB, JAS, AHM, LPM, SAG, and DRM contributed to data acquisition. PVD, JAS, AHM, IDP, QL, GP, DRM, and CLR contributed to the analysis of the data. SSB, JAS, AHM, LPM, IDP, AMN, JS, QL, GP, DRM, and CLR contributed to interpretation of the results. JAS, AHM, LPM, IDP, JS, and DRM contributed to drafting of the manuscript. SSB, PVD, JAS, AHM, LPM, IDP, AMN, JS, QL, BI, SAG, GP, DRM, and CLR contributed to critically reviewing or revising the manuscript. All authors had access to the data, were responsible for the decision to submit the manuscript, and agree to be accountable for all aspects of the work.

AJRCCM Articles in Press. Published March 30, 2023 as 10.1164/rccm.202211-2128LE

Descriptor: 9.15 Cough: Clinical

AJRCCM Articles in Press. Published March 30, 2023 as 10.1164/rccm.202211-2128LE

To the Editor:

Gefapixant is a P2X3 receptor antagonist that has demonstrated efficacy in COUGH-1 and COUGH-2, two Phase 3 trials for 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.

The current analysis evaluated a pooled dataset of both studies through 52 weeks of treatment. While gefapixant 45 mg BID demonstrated statistically significant

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improvement vs. placebo in primary and secondary endpoints during the main study periods, gefapixant 15 mg BID did not (1); therefore, the PRO and safety/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 lower quality of life, and a ≥1.3-point increase from baseline in the LCQ total score was considered to be 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 7 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 (LS) 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

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discontinuation due to a taste-related AE, and time to resolution of taste-related AEs were conducted.

Results

The pooled trial population included 2044 participants across 3 treatment arms. Of these, 1631 continued in the extension periods and 1534 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 2 treatment arms, 683 participants were treated with gefapixant 45 mg BID and 675 participants were treated with placebo.

LS Mean PROs in both the placebo and gefapixant groups improved over 52 weeks with numerically greater improvement observed with gefapixant 45 mg BID vs. placebo (Figure 1). The odds for achieving a clinically meaningful response were improved for gefapixant 45 mg BID vs placebo at each time point for each PRO (Figure 1).

At 52 weeks, there was a higher proportion of participants who reported ≥1 taste-related AE in the gefapixant 45-mg BID 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 due to a taste-related AE in the gefapixant 45-mg BID arm (95 of 683, 13.9%) than in the placebo arm (2 of 675, 0.3%). Of the discontinuations due to taste-related AEs in the gefapixant 45-mg BID group, half occurred during the initial 4 weeks of treatment.

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As previously reported, among 447 participants with taste-related AEs in the gefapixant 45 mg BID group, 429 (96%) had documented resolution as of database lock (1); 63% had resolution after discontinuation while 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 after database lock (as of December 2021) 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 BID, compared with placebo, achieved clinically meaningful improvements in PROs that were maintained over 52 weeks of treatment. In the gefapixant 45-mg BID 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, P2X2/3 heterotrimers, or both, on gustatory nerves are 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. While most of these AEs resolved after the last day of treatment, a quarter of participants had resolution while still taking gefapixant. And as previously observed, taste-related AEs were not considered

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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 or UCC, which are long-lasting conditions with a significant unmet need for safe and effective treatments.

ACKNOWLEDGMENTS

Medical writing support was provided by Anish Mehta of Merck & Co., Inc., Rahway, NJ, USA. We also thank Jennifer Pawlowski, MS, of Merck & Co., Inc., Rahway, NJ, USA, for editorial and administrative support. Additional editorial support was provided by Jenna Lewis, MA, ELS, of MedThink SciCom, Cary, NC, USA, and funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Data availability: The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA is available at

AJRCCM Articles in Press. Published March 30, 2023 as 10.1164/rccm.202211-2128LE

http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the Engage Zone site or via email to dataaccess@merck.com.

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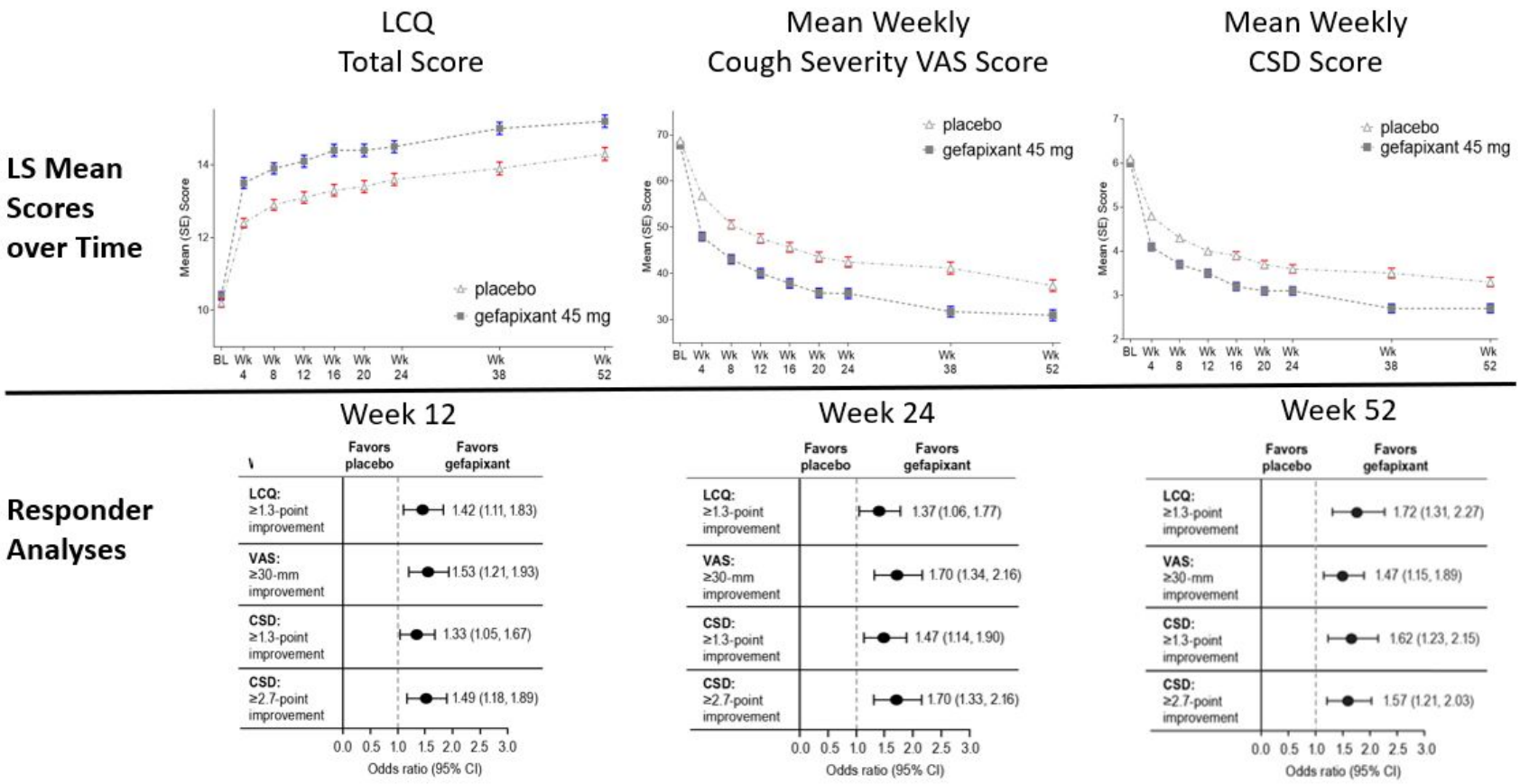
Figure 1. Mean (SE) PRO values over 52 weeks and odds ratios at Weeks 12, 24, and 52 for achieving clinically meaningful improvements in the LCQ total score, mean weekly cough severity VAS, and mean weekly CSD for gefapixant 45 mg BID vs placebo.



BID, twice daily; CSD, Cough Severity Diary; LCQ, Leicester Cough Questionnaire; VAS, visual analog scale.

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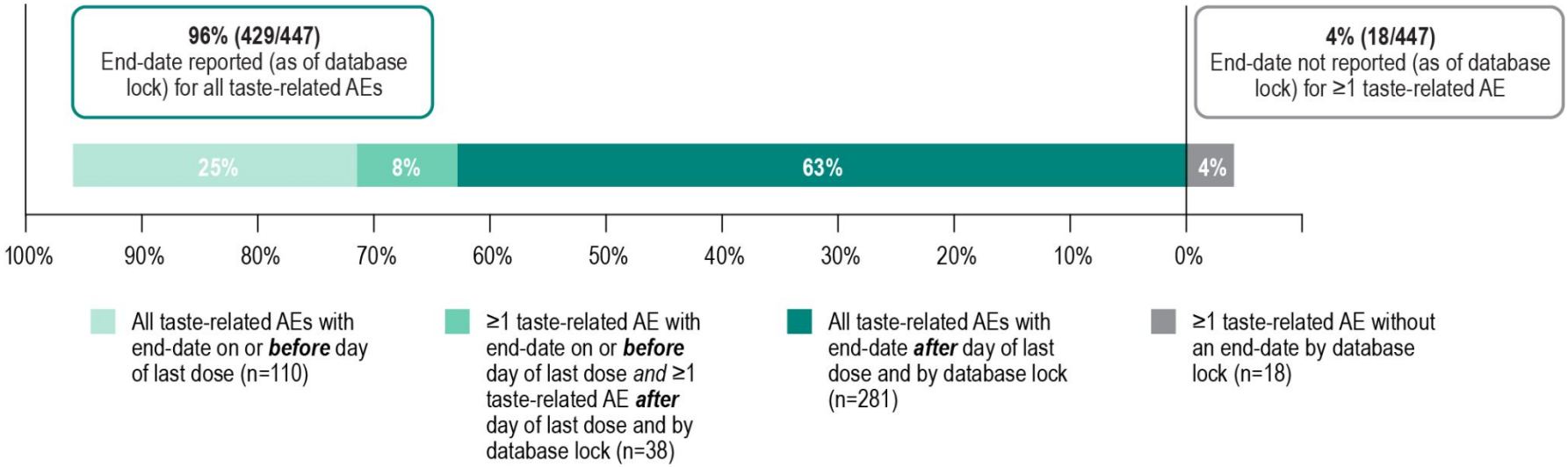
Figure 2. Resolution of taste-related AEs reported by 447 participants in the gefapixant 45-mg BID group.



AE, adverse event; BID, twice daily.

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