Efficacy and safety of gefapixant, a $P2X_3$ receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials

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Summary

Background Gefapixant is an oral $P2X_3$ receptor antagonist that has previously shown efficacy and safety in refractory chronic cough and unexplained chronic cough. We therefore aim to confirm the efficacy and safety of gefapixant in participants with refractory chronic cough and unexplained chronic cough.

Methods COUGH-1 and COUGH-2 were both double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. COUGH-1 was done in 156 sites in 17 countries and COUGH-2 in 175 sites in 20 countries. We enrolled participants who were 18 years or older with a diagnosis of refractory chronic cough or unexplained chronic cough of 1 year duration or more. Participants were also required to have a cough severity visual analogue scale score of 40 mm or more at screening and baseline. Eligible participants were randomly allocated (1:1:1), using a computer-generated allocation schedule, to one of three treatment groups: placebo, gefapixant 15 mg twice per day, or gefapixant 45 mg twice per day. All study treatments were given orally. Participants were treated over a 12-week main study period in COUGH-1 and a 24-week main study period in COUGH-2; followed by extension periods for a total of up to 52 weeks of treatment in both trials. The primary outcome was placebo-adjusted mean change in 24-h cough frequency at 12 weeks in COUGH-1 and 24 weeks in COUGH-2. Both studies were registered with ClinicalTrials.gov, NCT03449134 (COUGH-1) and NCT03449147 (COUGH-2).

Findings From March 14, 2018, (first participant screened) to July 26, 2019, (last participant screened) 732 patients were recruited in COUGH-1 and 1317 in COUGH-2. COUGH-1 randomly assigned and treated 730 participants (243 [33·3%] with placebo, 244 [33·4%] with gefapixant 15 mg twice per day, and 243 [33·3%] with gefapixant 45 mg twice per day); COUGH-2 randomly assigned and treated 1314 participants (435 [33·1%] with placebo, 440 [33·5%] with gefapixant 15 mg twice per day, and 439 [33·4%] with gefapixant 45 mg twice per day). Participants were mostly female (542 [74·2%] of 730 in COUGH-1 and 984 [74·9%] of 1314 in COUGH-2). The mean age was 59·0 years (SD 12·6) in COUGH-1 and 58·1 years (12·1) in COUGH-2, and the mean cough duration was 11·6 years (SD 9·5) in COUGH-1 and 11·2 years (9·8) in COUGH-2. Gefapixant 45 mg twice per day showed significant reductions in 24-h cough frequency compared with placebo at week 12 in COUGH-1 (18·5% [95% CI 32·9–0·9]; p=0·041) and at week 24 in COUGH-2 (14·6% [26·1–1·4]; p=0·031). Gefapixant 15 mg twice per day did not show a significant reduction in cough frequency versus placebo in both studies. The most common adverse events were related to taste disturbance: ageusia (36 [4·9%] of 730 in COUGH-1 and 86 [6·5%] of 1314 in COUGH-2), dysgeusia (118 [16·2%] in COUGH-1 and 277 [21·1%] in COUGH-2), hypergeusia (3 [0·4%] in COUGH-1 and 6 [0·5%] in COUGH-2), hypogeusia (19 [2·6%] in COUGH-1 and 80 [6·1%] in COUGH-2), and taste disorder (28 [3·8%] in COUGH-1 and 46 [3·5%] in COUGH-2).

Interpretation Gefapixant 45 mg twice per day is the first treatment to show efficacy with an acceptable safety profile in phase 3 clinical trials for refractory chronic cough or unexplained chronic cough.

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See **Online** for appendix

Introduction

Chronic cough, defined as cough lasting more than 8 weeks, is a common condition with a worldwide prevalence of approximately 5–10%, accounting for up to 38% of outpatient pulmonary consultations in the USA.[1,2] Guidelines recommend medical evaluation and trials of therapy directed at common causes, including asthma, gastroesophageal reflux disease, and allergic rhinitis, after the exclusion of malignancy, infection, smoking, or medications associated with cough.[3–5] Among patients with chronic cough who seek medical attention at specialty care clinics, up to 40% of these patients are

Research in context

Evidence before this study

We searched PubMed with the terms "$P2X_3$" and "chronic cough" in July 2, 2020. We had no restrictions on article type, language, or date of publication. We found 31 articles. Effective pharmacological treatment of chronic cough is an unmet medical need. The involvement of purinergic signalling in chronic cough is a promising target for effective treatments. A previous phase 2 study of gefapixant, a $P2X_3$ receptor antagonist, at a dose of 600 mg showed a significant reduction in cough frequency compared with placebo in patients with refractory chronic cough. A phase 2b study in 253 participants with refractory chronic cough or unexplained chronic cough showed a significant reduction in cough frequency compared with placebo with gefapixant 50 mg twice per day. These trials led to the initiation of the phase 3 randomised controlled trials (COUGH-1 and COUGH-2), with a total of more than 2000 participants.

Added value of this study

COUGH-1 and COUGH-2 are the first phase 3 randomised controlled trials evaluating treatments for chronic cough. Efficacy is reported for 12 weeks in COUGH-1 and 24 weeks in COUGH-2, and we report safety findings for up to 52 weeks of treatment with placebo, gefapixant 15 mg twice per day, or gefapixant 45 mg twice per day. The gefapixant 45 mg twice per day dose showed clinically meaningful reduction in cough frequency that was significantly superior to placebo.

Implications of all the available evidence

The results of these phase 3 trials support the therapeutic value of gefapixant for patients with refractory chronic cough or unexplained chronic cough.

estimated to have cough that remains uncontrolled despite comprehensive investigation and treatment of comorbid conditions and therefore might be a closer approximation of the subset of patients with refractory chronic cough and unexplained chronic cough.[1,6,7] Patients for whom no cause can be determined despite extensive evaluation are considered to have unexplained chronic cough.[8] Refractory chronic cough or unexplained chronic cough might persist for years, causing considerable distress and impaired health status.[9,10] Currently, no licensed treatments for refractory chronic cough or unexplained chronic cough exists, and patients often resort to off-label therapy despite little evidence for efficacy and the potential for adverse effects.

Patients with chronic cough typically report an irritating sensation in the throat and have coughing episodes triggered by relatively innocuous stimuli including changes in temperature, talking, laughing, or exposure to environmental irritants (eg, aerosol sprays, perfume, or scents).[11] These clinical characteristics suggest a dysregulation of sensory neurons leading some to propose the concept of a so-called cough hypersensitivity syndrome to describe this clinical condition.[12] Targeting of peripheral and central neuronal receptors to attenuate neural hyperexcitability represents a potential therapeutic strategy.[13]

$P2X_3$ receptors are ATP-gated ion channels found on sensory C-fibres of the vagus nerve. C-fibres are activated in response to inflammation or chemical irritants to initiate a cough reflex. In the airways, ATP can be released from epithelial cells in response to stimuli including injury, inflammation, and viral infection.[14,15] Binding of extracellular ATP to $P2X_3$ receptors is sensed as a damage signal by C-fibres.[16] Thus, cough observed in refractory chronic cough and unexplained chronic cough is potentially related to excessive activation of C-fibres via binding of extracellular ATP to $P2X_3$ receptors. Gefapixant is a $P2X_3$ receptor antagonist, which also has activity against the $P2X_{2/3}$ receptor subtype, and has been found to reduce cough responses to inhaled ATP.[17] Clinically meaningful and dose-related reductions in cough frequency have been shown with gefapixant in phase 2 studies. These studies have also shown improvements in patient-reported outcomes and health-related quality of life.[18–20]

In light of the aforementioned, we aim to confirm the efficacy and safety of gefapixant in participants with refractory chronic cough and unexplained chronic cough.

Methods

Study design and participants

COUGH-1 and COUGH-2 were both double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. COUGH-1 was done in 156 primary, secondary, and tertiary care sites in 17 countries and COUGH-2 was done in 175 sites in 20 countries. We enrolled participants who were 18 years or older with chronic cough of 1 year duration or more in these studies. Participants were also required to have self-rated their cough severity, using a 100-mm visual analogue scale (ranging from 0 [ie, no cough] to 100 [ie, extremely severe cough]) as at least 40 mm at both screening and baseline visits. Participants must have had no substantial abnormalities on chest radiograph or CT scan of the thorax within 5 years of study participation and after the onset of cough contributing to chronic cough. Major exclusion criteria were active or recent (ie, within 12 months) smoking, angiotensin converting enzyme inhibitor treatment within 3 months, and a FEV_1/FVC ratio of less than 60% within a year of the study. Further details about the inclusion and exclusion criteria were previously published.[21]

The primary investigators verified diagnosis of refractory chronic cough or unexplained chronic cough according to the American College of Chest Physicians'

(ACCP) guidelines.[1,22] Refractory chronic cough was defined as cough that persisted in participants with a comorbid condition related to cough (eg, gastroesophageal reflux disease, asthma, or allergic rhinitis) who received appropriate diagnostic work-up and therapy for at least 2 months for known conditions according to ACCP guidelines. Unexplained chronic cough was defined as chronic cough in participants who had a clinical evaluation per ACCP guidelines that did not suggest a comorbid condition related to cough.

COUGH-1 and COUGH-2 were approved by local institutional review boards and principles of Good Clinical Practice were followed. We obtained written informed consent from all participants.

Randomisation and masking

Randomisation and masking for these trials have been previously described.[21] Briefly, eligible participants were randomly allocated (1:1:1) to one of three treatment groups: placebo, gefapixant 15 mg twice per day, or gefapixant 45 mg twice per day. The randomisation was stratified by sex and geographical region and was done by a centralised interactive voice or web response system. The randomisation schedule was computer generated. These studies used a double-blind design in which patients and all personnel involved with the conduct and the interpretation of the study were masked to study treatment. Randomisation data were kept strictly confidential, filed securely at Merck & Co (Kenilworth, NJ, USA), and were accessible only to authorised individuals until the time of unmasking. Unmasking by an interactive voice or web response system was available 24 h per day, 7 days per week in the case of an emergency only, when knowledge of the investigational product was essential for the welfare of a patient.

Procedures

Participants were screened over a period of a minimum of 7 days and up to approximately 14 days. At baseline, eligible participants who were randomly allocated to either placebo, gefapixant 15 mg twice per day, or gefapixant 45 mg twice per day had initial outcome measurements taken. All study treatments were given orally. The doses used in this study were selected based on previous phase 2 studies, exposure-response data, and modelling and simulation as described previously.[21] Participants were treated over a 12-week main study period in COUGH-1 and a 24-week main study period in COUGH-2 followed by extension periods in both trials during which participants continued their same therapy for a total of up to 52 weeks of treatment. Participants were followed-up for 14 days after last visit to ensure adequate collection of adverse events. Cough frequency was measured for 24 h at baseline and on study visit days (day 28, day 56, and day 84 in COUGH-1 and COUGH-2, as well as day 112, day 140, and day 168 in COUGH-2) using an ambulatory audio recording device (VitaloJAK cough monitor; Vitalograph, Ennis, UK) that uses two microphones: a sternum contact sensor used to record sounds from the lungs and trachea and a lapel air microphone that allows the device to distinguish ambient sounds from coughs originating from the participant.[23] Digital recordings from the VitaloJAK monitor were processed in Vitalograph's centralised reading centre. The recordings were condensed using a computer algorithm to remove periods of silence and periods with no cough sounds. Two independent human analysts then reviewed both audio recordings and visual waveforms that show a characteristic explosive phase followed by an auditory phase to identify and mark individual coughs that occurred over the 24 h period (appendix p 5).

Patient-reported outcomes were captured with the use of electronic diaries, which were completed daily and monitored by the investigator for compliance. Participants were instructed to bring their electronic diaries to study visits. The Leicester Cough Questionnaire was completed in the electronic diaries in the evening on the day of study visits. The cough severity visual analogue scale and Cough Severity Diary were completed in electronic diaries daily. Adverse events were recorded by participants on comment cards between study visits and assessed, documented, and reported on electronic case report forms by the investigators at each study visit.

Outcomes

The primary efficacy outcomes were 24-h cough frequency—reported as coughs per h—through week 12 in COUGH-1 and week 24 in COUGH-2, and were analysed as change from baseline on the natural log scale.[23] Several subgroup analyses were prespecified for the primary endpoint. These included sex (male and female), region (North America, Europe, Asia-Pacific, and others), age group (<60 years *vs* ≥60 years and <65 years *vs* ≥65 years), duration of cough (<10 years and ≥10 years), baseline cough severity visual analogue scale (<60 mm and ≥60 mm), baseline 24-h cough frequency (<20 coughs per h and ≥20 coughs per h), and primary diagnosis (refractory chronic cough and unexplained chronic cough).

Secondary outcomes with hypothesis testing and multiplicity adjustment were change from baseline in awake cough frequency (coughs per h during waking hours) and the proportion of participants with 30% reduction or more in 24-h cough frequency.[24] The proportion of participants with a 1·3-point increase or more (ie, clinically meaningful improvement[25]) for the Leicester Cough Questionnaire was a key secondary outcome in COUGH-2. Outcomes not subject to hypothesis testing were the proportion of participants achieving the following: 1·3-point increase or more in total score of the Leicester Cough Questionnaire in COUGH-1, 1·3-point or more or 2·7-point or more reduction in the total score of the Cough Severity Diary,

and 30 mm reduction or more in the cough severity visual analogue scale.[26] Responder analyses for 24-h cough frequency at 50% and 70% reductions were exploratory endpoints. Additional exploratory outcome measures, which will be reported separately, have been described previously.[21]

Adverse events were assessed by clinical evaluation. Other study parameters including vital signs, physical examination, and laboratory safety tests were also evaluated. Investigators determined relationship of adverse events to study medication, intensity, and seriousness. Taste-related adverse events (ie, ageusia, dysgeusia, hypergeusia, hypogeusia, and taste disorder) were predefined as adverse events of special interest for prespecified statistical analyses to evaluate treatment group differences (gefapixant *vs* placebo).[21]

Statistical analysis

The primary hypothesis was that one or more doses of gefapixant was superior to placebo in reducing cough frequency over 24 h at week 12 in COUGH-1 and week 24 in COUGH-2. We report the primary data that includes efficacy from the main study periods and safety over 52 weeks. Hypothesis testing followed a step-down multiplicity adjustment in which treatment-group comparisons were done in a specific order until no significant difference from placebo was observed. p values for prespecified hypotheses are provided following the multiplicity strategy. Further details about the multiplicity strategy are described in the appendix (pp 6–7).

Cough frequency endpoints were log transformed and results are therefore displayed as geometric means, because of skewed data typical of cough trials and to account for the disproportionally large numbers of coughs sometimes observed in patients with refractory chronic cough or unexplained chronic cough. The primary endpoint was evaluated using a longitudinal ANCOVA model, which included response variable of change from baseline in log-transformed cough frequency and covariates for treatment, visit, interaction of treatment by visit, sex, region, the log-transformed baseline value, and the interaction of log-transformed baseline cough frequency by visit.

Analysis of efficacy endpoints was done in the full analysis set, in which all participants who have taken at least one dose (including those who did not complete the evaluation period) contribute to the model. Analysis of safety was evaluated in the all-participants-as-treated population, which consisted of all randomly allocated participants who received at least one dose of study treatment, in which participants are classified based on treatment received.

The studies were planned to have sample sizes of 720 in COUGH-1 and 1290 in COUGH-2. COUGH-1 was powered for pairwise comparisons for gefapixant 45 mg twice per day versus placebo at around 90% or higher for 12-week 24-h cough frequency, awake cough frequency, and the percentage of participants with a 30% reduction or more in 24-h cough frequency. For 15 mg twice per day versus placebo, COUGH-1 was powered at around 90% for 12-week 24-h cough frequency and around 80% for awake cough frequency; the study was not powered to evaluate gefapixant 15 mg twice per day versus placebo for the 30% reduction or more in 24-h cough frequency endpoint. COUGH-2 was powered for pairwise comparisons for both gefapixant 45 mg twice per day and gefapixant 15 mg twice per day versus placebo at more than 90% for 24-week 24-h cough frequency and awake cough frequency; COUGH-2 was powered for pairwise comparisons for gefapixant 45 mg twice per day versus placebo for the percentage of participants with a 1·3-point increase or more in the total score of the Leicester Cough Questionnaire relative to baseline at around 80%, but the study was not powered for gefapixant 15 mg twice per day versus placebo for this endpoint. COUGH-2 was not powered to evaluate the 30% reduction or more in 24-h cough frequency endpoint. The effect size in the sample size calculations is based on the observed data for the same endpoint in the phase 2b trial.[20] Specifically, the assumptions for the 24-h coughs per h at week 12 in COUGH-1 and week 24 in COUGH-2 are as follows: relative reduction in change from baseline in 24-h coughs per h at week 12 was 20% in gefapixant 15 mg twice per day and at week 24 was 30% in gefapixant 45 mg twice per day, common standard deviation of the change from baseline in log-transformed 24-h coughs per h was 0·7, and the number of coughs per h follows approximately a log-normal distribution. The sample size is jointly driven by the primary and all the key secondary efficacy endpoints.

To minimise missing data, participants who discontinued treatment were encouraged to stay in the study with efficacy data collected and included in the analysis. The longitudinal ANCOVA model was a likelihood-based method, which uses all observed data with no imputation for missing data in the primary analysis. Sensitivity analyses were also done based on the missing-not-at-random assumptions including Tipping Point and Jump to Reference analyses (appendix pp 15–16).

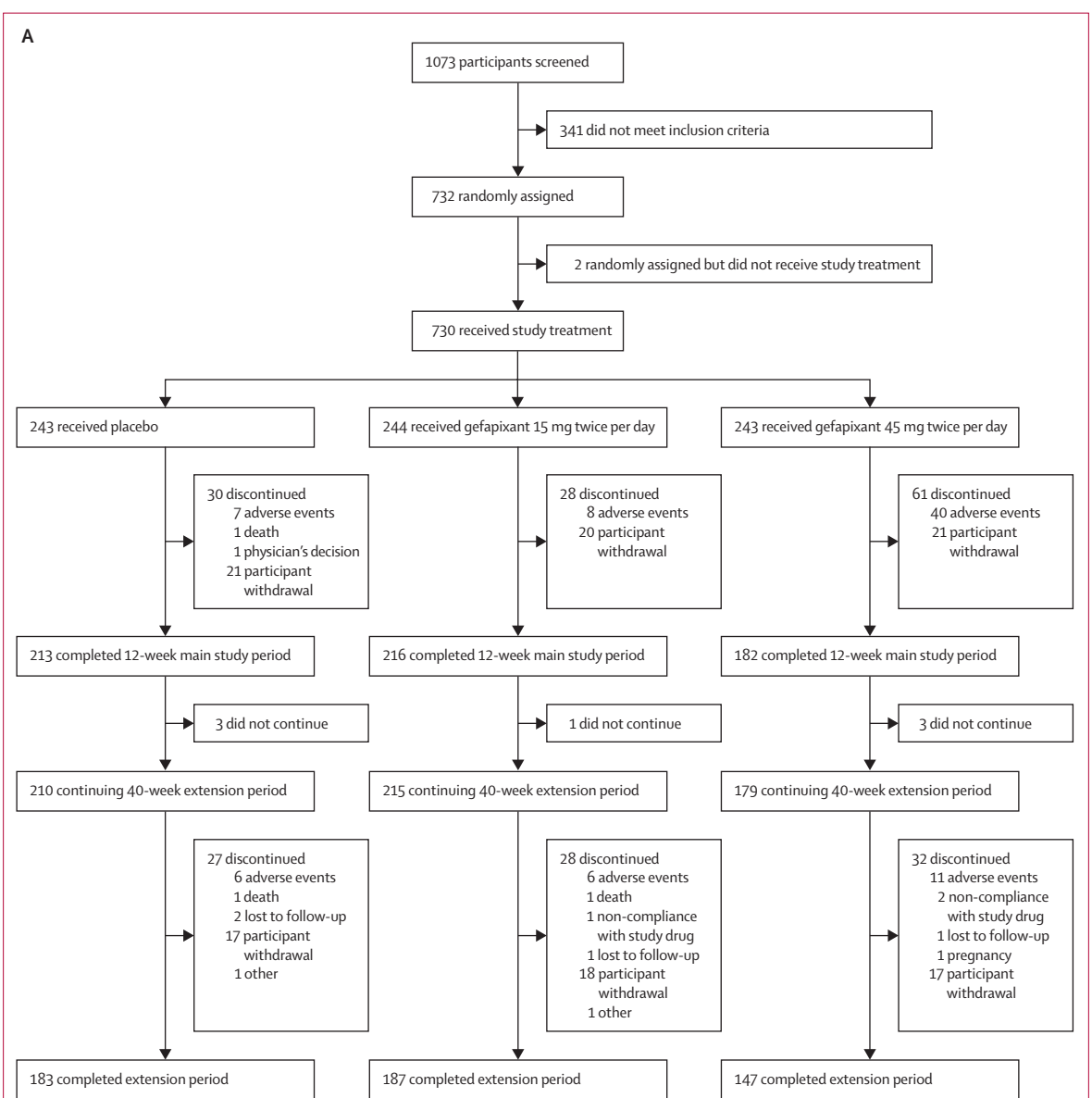
Participant data from COUGH-1 and COUGH-2 were pooled for the analysis of patient subgroups. Analysis in the pooled dataset were done with the same methods for the individual trials with an additional covariate identifying the trial for which the participant was enrolled (ie, COUGH-1 or COUGH-2). No hypothesis testing was conducted for the pooled analyses and the results were for estimation purposes only.

Continuous secondary efficacy endpoints were analysed using a similar longitudinal ANCOVA model as used for the primary efficacy analysis. The awake cough frequency data were log-transformed (natural log) before analysis. Responder end-points were analysed by the logistic regression model including

terms for treatment, visit, the interaction of treatment by visit, sex, region, baseline, and the interaction of baseline by visit for the underlying continuous response. Log odds ratio (OR) were back transformed into OR for final reporting.

Safety evaluation was based on cumulative data collected across both the main and extension study periods and were assessed by clinical review of all relevant parameters including adverse events, laboratory tests, vital signs, and ECG measurements. Taste-related adverse events were subject to inferential testing, and broad clinical and laboratory adverse event categories were evaluated via point estimates and 95% CIs for between-group comparisons. No major changes in the study population or treatments occurred in the protocol amendment. The criterion for estimated glomerular filtration rate was updated after the start of the studies and was based on a study suggesting that an increased risk for relevant adverse events was not anticipated.[18] The statistical analysis plan for COUGH-2 was updated before database lock with regard to the multiplicity strategy to allow for hypothesis testing of the gefapixant 45 mg twice per day group for secondary endpoints before testing the gefapixant 15 mg twice per day group for the primary endpoint (appendix pp 6–7).

We did all statistical analyses using SAS (version 9.4). Both studies were registered with ClinicalTrials.gov, NCT03449134 (COUGH-1) and NCT03449147 (COUGH-2).



(Figure 1 continues on next page)

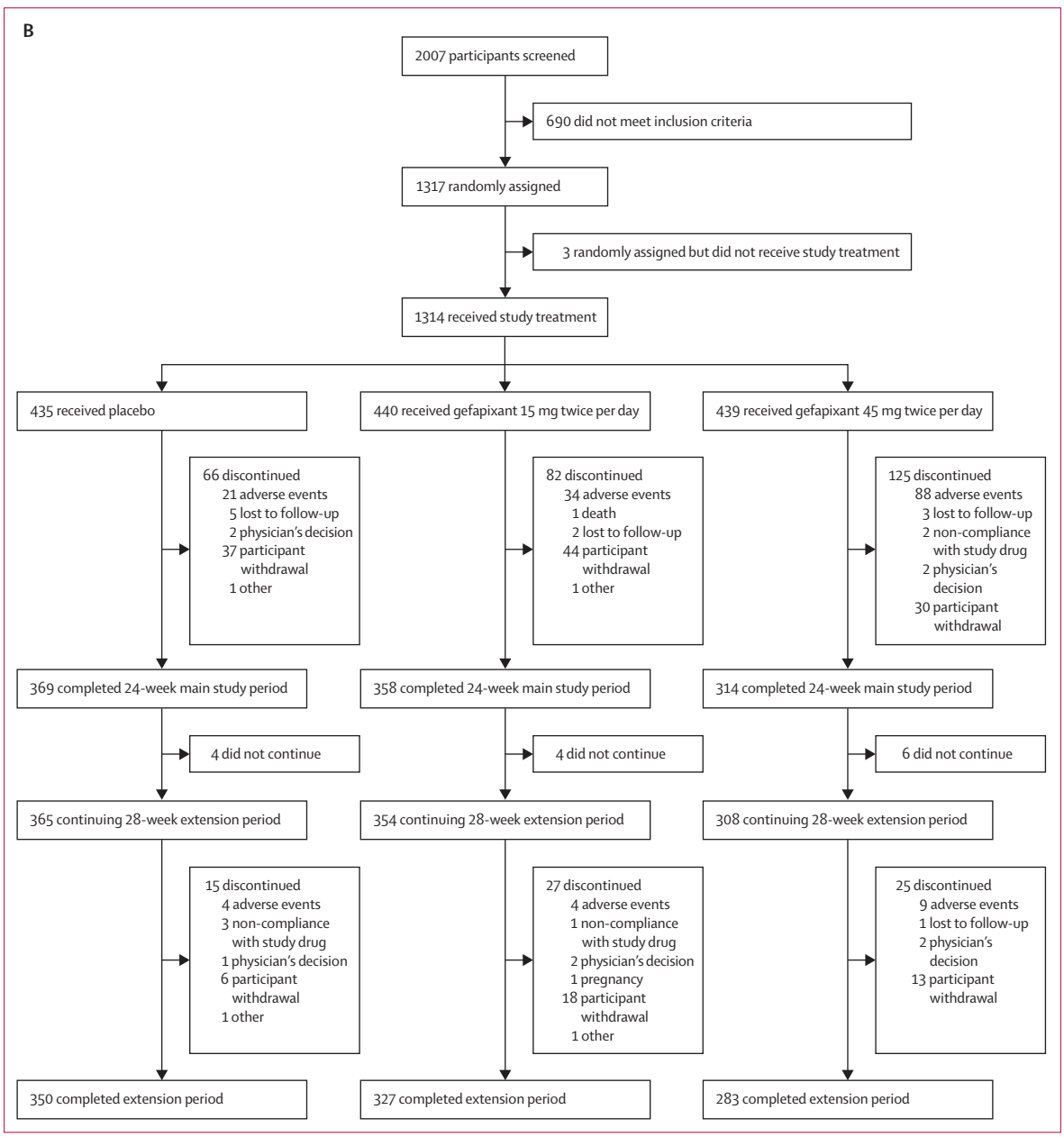


Figure 1: **Trial profiles showing participant disposition for COUGH-1 and COUGH-2**
(A) The main study period for COUGH-1 was 12 weeks with a 40-week blinded extension period. (B) The main study period for COUGH-2 was 24 weeks with a 28-week blinded extension period.

Role of the funding source
Academic advisors and representatives of the funder participated in the study design. Data collected by the investigators and their site personnel were analysed and interpreted by senior academic authors and representatives of the funder. The funder provided results and methodological details.

Results
The 12-week main study of COUGH-1 was done from April 3, 2018, (first participant randomly assigned) to Oct 1, 2019, (main-study database lock) in 156 global sites; the 40-week extension period was completed on June 5, 2020 (last participant, last visit). In COUGH-1, 732 participants were randomly assigned to treatment groups and 730 were treated (243 [33·3%] with placebo, 244 [33·4%] with gefapixant 15 mg twice per day, and 243 [33·3%] with gefapixant 45 mg twice per day). The 24-week main study of COUGH-2 was done from March 15, 2018, (first participant randomly assigned) to March 4, 2020, (24-week main study database lock) in 175 global sites; the 28-week extension

period was completed on Aug 20, 2020. In COUGH-2, 1317 participants were randomly assigned to treatment groups and 1314 were treated (435 [33·1%] with placebo, 440 [33·5%] with gefapixant 15 mg twice per day, and 439 [33·4%] with gefapixant 45 mg twice per day). Figure 1 shows the number of participants completing or discontinuing the studies. The most common reasons for discontinuation were adverse events and withdrawal by participant (ie, decision to discontinue made between the investigator and participant because of inability to comply with the protocol requirements or other patient-relevant reasons not otherwise captured; figure 1).

Baseline demographics and cough characteristics of study participants were balanced between treatment allocations in both studies (table 1); these findings were consistent with previous trials in patients with chronic cough. Most participants were female (542 [74·2%] of 730 in COUGH-1 and 984 [74·9%] of 1314 in COUGH-2). The mean age was 59·0 years (SD 12·6) in COUGH-1 and 58·1 years (12·1) in COUGH-2, and the mean cough duration was 11·6 years (SD 9·5) in COUGH-1 and 11·2 years (9·8) in COUGH-2. The highest proportion of participants were from Europe (365 [50·0%] of 730 in COUGH-1 and 715 [54·4%] of 1314 in COUGH-2) and North America (167 [22·9%] in COUGH-1 and 294 [22·4%] in COUGH-2; table 1). Other baseline characteristics reported suggest that the patient population has a high cough frequency, high self-reported cough severity, and a long history of chronic cough. In COUGH-1, 428 (58·6%) of 730 participants were diagnosed with refractory chronic cough and 302 (41·4%) were diagnosed with unexplained chronic cough; in COUGH-2, 829 (63·1%) of 1314 participants were diagnosed with refractory chronic cough and 485 (36·9%) were diagnosed with unexplained chronic cough (table 1).

The most common comorbid conditions associated with cough included asthma (297 [40·7%] of 730 in COUGH-1 and 528 [40·2%] of 1314 in COUGH-2), gastroesophageal reflux disease (296 [40·5%] in COUGH-1 and 530 [40·3%] in COUGH-2), and allergic rhinitis (144 [19·7%] in COUGH-1 and 191 [14·5%] in COUGH-2). Previous medication classes included medications for acid-related disorders (eg, esomeprazole or omeprazole; 436 [59·7%] of 730 in COUGH-1 and 683 [52·0%] of 1314 in COUGH-2), anti-inflammatory or anti-infective medications including steroids (eg, budesonide or prednisolone; 252 [34·5%] in COUGH-1 and 363 [27·6%] in COUGH-2), and analgesics including neuromodulators to manage chronic cough (eg, codeine, gabapentin, or morphine; 355 [48·6%] in COUGH-1 and 508 [38·7%] COUGH-2).

In both studies, gefapixant 45 mg twice per day was superior to placebo in significantly reducing 24-h cough frequency after 12 weeks in COUGH-1 and 24 weeks in COUGH-2. In COUGH-1, the model-based estimated reduction in 24-h cough frequency from baseline to week 12 was 53% (95% CI 46–59) in the placebo group,

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day	Total
COUGH-1				
Number of participants	243	244	243	730
Sex				
Female	181 (74·5%)	181 (74·2%)	180 (74·1%)	542 (74·2%)
Male	62 (25·5%)	63 (25·8%)	63 (25·9%)	188 (25·8%)
Age (years)				
Mean	57·9 (13·1)	59·6 (11·7)	59·4 (13·1)	59·0 (12·6)
Range	21–81	22–89	19–85	19–89
Race				
American Indian or Alaska native	7 (2·9%)	6 (2·5%)	8 (3·3%)	21 (2·9%)
Asian	35 (14·4%)	35 (14·3%)	34 (14·0%)	104 (14·2%)
Black or African American	4 (1·6%)	3 (1·2%)	4 (1·6%)	11 (1·5%)
Multiple	8 (3·3%)	5 (2·0%)	11 (4·5%)	24 (3·3%)
White	189 (77·8%)	195 (79·9%)	186 (76·5%)	570 (78·1%)
Duration of chronic cough (years)				
Mean	11·7 (9·9)	11·8 (9·1)	11·2 (9·4)	11·6 (9·5)
Range	2–59	2–45	2–56	2–59
Region				
Asia-Pacific	35 (14·4%)	34 (13·9%)	34 (14·0%)	103 (14·1%)
Europe	121 (49·8%)	123 (50·4%)	121 (49·8%)	365 (50·0%)
North America	56 (23·0%)	55 (22·5%)	56 (23·0%)	167 (22·9%)
Others	31 (12·8%)	32 (13·1%)	32 (13·2%)	95 (13·0%)
Primary diagnosis				
Refractory chronic cough	148 (60·9%)	141 (57·8%)	139 (57·2%)	428 (58·6%)
Unexplained chronic cough	95 (39·1%)	103 (42·2%)	104 (42·8%)	302 (41·4%)
Mean HARQ at baseline	40·2 (13·6)	39·4 (13·3)	39·3 (13·0)	39·6 (13·3)
Baseline values for efficacy endpoints				
24-h cough frequency				
Geometric mean coughs per h	22·0	19·7	17·7	19·7
Leicester Cough Questionnaire total score				
Mean baseline total score	10·0 (3·1)	10·5 (2·9)	10·5 (2·7)	10·3 (2·9)
Cough severity visual analogue scale (mm)				
Weekly mean	69·1 (13·9)	68·2 (15·0)	67·9 (12·8)	68·4 (13·9)
Cough Severity Diary score				
Weekly mean	6·2 (1·5)	6·1 (1·7)	6·1 (1·5)	6·1 (1·6)
COUGH-2				
Number of participants	435	440	439	1314
Sex				
Female	326 (74·9%)	329 (74·8%)	329 (74·9%)	984 (74·9%)
Male	109 (25·1%)	111 (25·2%)	110 (25·1%)	330 (25·1%)
Age (years)				
Mean	58·0 (12·6)	58·6 (11·4)	57·8 (12·4)	58·1 (12·1)
Range	19–84	22–88	19–87	19–88
Race				
American Indian or Alaska native	20 (4·6%)	28 (6·4%)	24 (5·5%)	73 (5·6%)
Asian	15 (3·4%)	14 (3·2%)	15 (3·4%)	44 (3·3%)
Black or African American	5 (1·1%)	9 (2·0%)	14 (3·2%)	28 (2·1%)
Native Hawaiian or other Pacific Islander	4 (0·9%)	2 (0·5%)	3 (0·7%)	9 (0·7%)

(Table 1 continues on next page)

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day	Total
(Continued from previous page)				
Multiple	36 (8·3%)	31 (7·0%)	37 (8·4%)	104 (7·9%)
White	355 (81·6%)	356 (80·9%)	346 (78·8%)	1057 (80·4%)
Duration of chronic cough (years)				
Mean	10·7 (8·8)	11·9 (10·7)	10·9 (9·9)	11·2 (9·8)
Range	2–51	1–75	2–65	1–75
Region				
Asia-Pacific	26 (6·0%)	27 (6·1%)	28 (6·4%)	81 (6·2%)
Europe	238 (54·7%)	238 (54·1%)	239 (54·4%)	715 (54·4%)
North America	97 (22·3%)	99 (22·5%)	98 (22·3%)	294 (22·4%)
Others	74 (17·0%)	76 (17·3%)	74 (16·9%)	224 (17·0%)
Primary diagnosis				
Refractory chronic cough	277 (63·7%)	273 (62·0%)	279 (63·6%)	829 (63·1%)
Unexplained chronic cough	158 (36·3%)	167 (38·0%)	160 (36·4%)	485 (36·9%)
Mean HARQ at baseline	40·1 (13·2)	39·3 (13·7)	39·6 (13·5)	39·7 (13·5)
Baseline values for efficacy endpoints				
24-h cough frequency				
Geometric mean coughs per h	19·4	18·9	18·5	18·9
Leicester Cough Questionnaire total score				
Mean baseline total score	10·3 (3·0)	10·4 (3·0)	10·4 (3·0)	10·4 (3·0)
Cough severity visual analogue scale (mm)				
Weekly mean	68·5 (14·3)	67·4 (14·8)	67·7 (13·9)	67·8 (14·3)
Cough Severity Diary score				
Weekly mean	6·0 (1·6)	5·9 (1·8)	6·0 (1·6)	5·9 (1·7)

Data are n, n (%), mean (SD), or range. HARQ=Hull Airway Reflux Questionnaire.

Table 1: **Baseline patient characteristics**

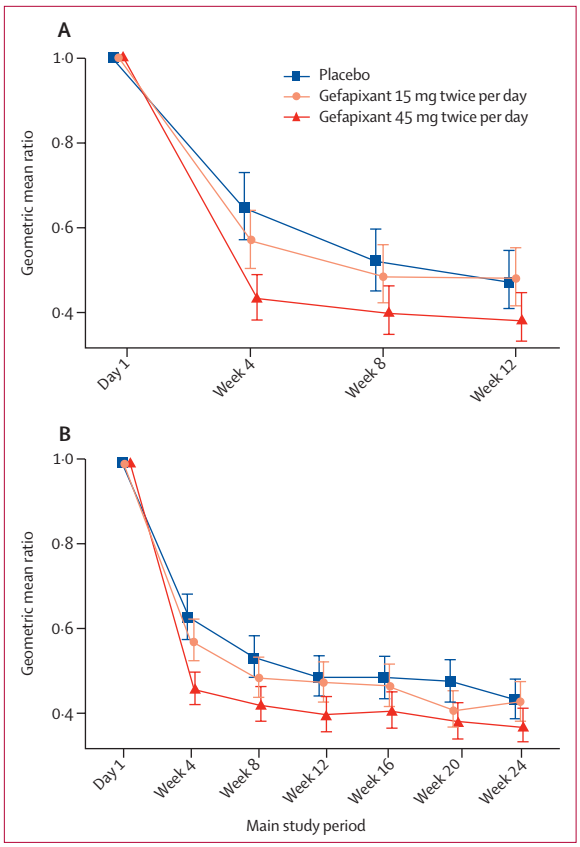


Figure 2: **24-h cough frequency over 12 weeks in COUGH-1 (A) and 24 weeks in COUGH-2 (B)**
Error bars are 95% CIs.

52% (45–59) in the gefapixant 15 mg twice per day group, and 62% (56–67) in the gefapixant 45 mg twice per day group. The estimated relative reduction versus placebo in 24-h cough frequency at week 12 (ie, the primary endpoint) was 18·5% (95% CI 0·9 to 32·9; p=0·041) for gefapixant 45 mg twice per day and –1·6% (95% CI –23·0 to 16·1; p=0·87) for gefapixant 15 mg twice per day. In COUGH-2, the model-based estimated reduction in 24-h cough frequency from baseline to week 24 was 57% (95% CI 52–61) in the placebo group, 57% (53–62) in the gefapixant 15 mg twice per day group, and 63% (59–67) in the gefapixant 45 mg twice per day group. The estimated relative reduction versus placebo in 24-h cough frequency at week 24 (ie, the primary endpoint) was 14·6% (95% CI 1·4 to 26·1; p=0·031) for gefapixant 45 mg twice per day and 1·1% (95% CI –14·0 to 14·3; p=0·88) for gefapixant 15 mg twice per day. Cough frequency reduction was evident at the first evaluation at week 4 and increased through week 12 for COUGH-1 and week 24 for COUGH-2 (figure 2).

The predefined subgroup analyses were supportive of the primary endpoint and generally showed consistency in 24-h cough frequency reductions at 12 weeks (figure 3). Moderately greater differences from placebo were observed in the subgroup of higher baseline cough severity (ie, cough severity visual analogue scale ≥60 mm).

In COUGH-2, the OR for a 1·3-point increase or more in the Leicester Cough Questionnaire total score was significantly greater for gefapixant 45 mg twice per day than for placebo (OR 1·41 [95% CI 1·02 to 1·96]; p=0·040; table 2). Additionally, in COUGH-2 compared with placebo, gefapixant 45 mg twice per day showed a significant reduction from baseline in awake cough frequency by week 24 (estimated relative reduction 15·79% [95% CI 2·50–27·27]; p=0·02; table 2). Figure 4 shows proportions of participants with 30%, 50%, and 70% reductions in cough frequency; the difference between gefapixant 45 mg twice per day and placebo increases with increasingly stringent criteria: differences of 4·0% for 30% reduction, 7·8% for 50% reduction, and 8·2% for 70% reduction at 12 weeks in COUGH-1 and 6·0% for 30% reduction, 7·4% for 50% reduction, and 7·9% for 70% reduction at 24 weeks in COUGH-2.

Safety data during the main study periods are presented in the appendix (pp 8–11). Briefly, overall adverse events during the main study periods occurred in 447 (61·2%) of 730 participants after 12 weeks in COUGH-1 and 1044 (79·5%) of 1314 participants after 24 weeks in COUGH-2.

Discontinuations due to adverse events occurred in seven (2·9%) of 243 participants receiving placebo, eight (3·3%) of 244 receiving gefapixant 15 mg twice per day, and 41 (16·9%) of 243 receiving gefapixant 45 mg twice per day in COUGH-1 by 12 weeks and 21 (4·8%) of 435 participants receiving placebo, 34 (7·7%) of 440 receiving gefapixant 15 mg twice per day, and 88 (20·0%) of 439 receiving gefapixant 45 mg twice per day in COUGH-2 by 24 weeks. Serious adverse events occurred in 19 (2·6%) of 730 participants and were balanced between treatment groups by 12 weeks in COUGH-1; serious adverse events occurred in 43 (3·2%) of 1314 participants by 24 weeks in COUGH-2.

For the 52-week period, overall adverse events occurred in 578 (79·2%) of 730 participants in COUGH-1 and 1121 (85·3%) of 1314 in COUGH-2. By week 52, discontinuations due to adverse events occurred in 13 (5·3%) of 243 participants receiving placebo, 14 (5·7%) of 244 receiving gefapixant 15 mg twice per day, and 52 (21·4%) of 243 receiving gefapixant 45 mg twice per day in COUGH-1 and 25 (5·7%) of 435 participants receiving placebo, 38 (8·6%) of 440 receiving gefapixant 15 mg twice per day, and 97 (22·1%) of 439 receiving gefapixant 45 mg twice per day in COUGH-2. Taste-related adverse events were the most common adverse events in participants receiving gefapixant 45 mg twice per day. Taste-related adverse events occurred in 11 (4·5%) of 243 participants receiving placebo, 31 (12·7%) of 244 receiving gefapixant 15 mg twice per day, and 144 (59·3%) of 243 receiving gefapixant 45 mg twice per day in COUGH-1 and 36 (8·3%) of 432 participants receiving placebo, 89 (20·1%) of 442 receiving gefapixant 15 mg twice per day, and 303 (68·9%) of 440 receiving gefapixant 45 mg twice per day in COUGH-2 by 52 weeks (table 3).

The majority of taste-related adverse events were mild or moderate in intensity and reversed upon cessation of therapy. Among participants with taste-related adverse events while receiving gefapixant 45 mg twice per day, 429 (96·0%) of 447 had resolution of their taste-related adverse events; 110 (24·6%) of those with taste-related adverse events on gefapixant 45 mg twice per day had resolution while on treatment (median time to resolution of 65 days during treatment [IQR 28–171]) rather than after discontinuation (median time to resolution of 5 days after the final dose [3–15]). The median time to onset of taste-related adverse events was 2 days (1–5) overall in both studies among participants receiving gefapixant 45 mg twice per day;

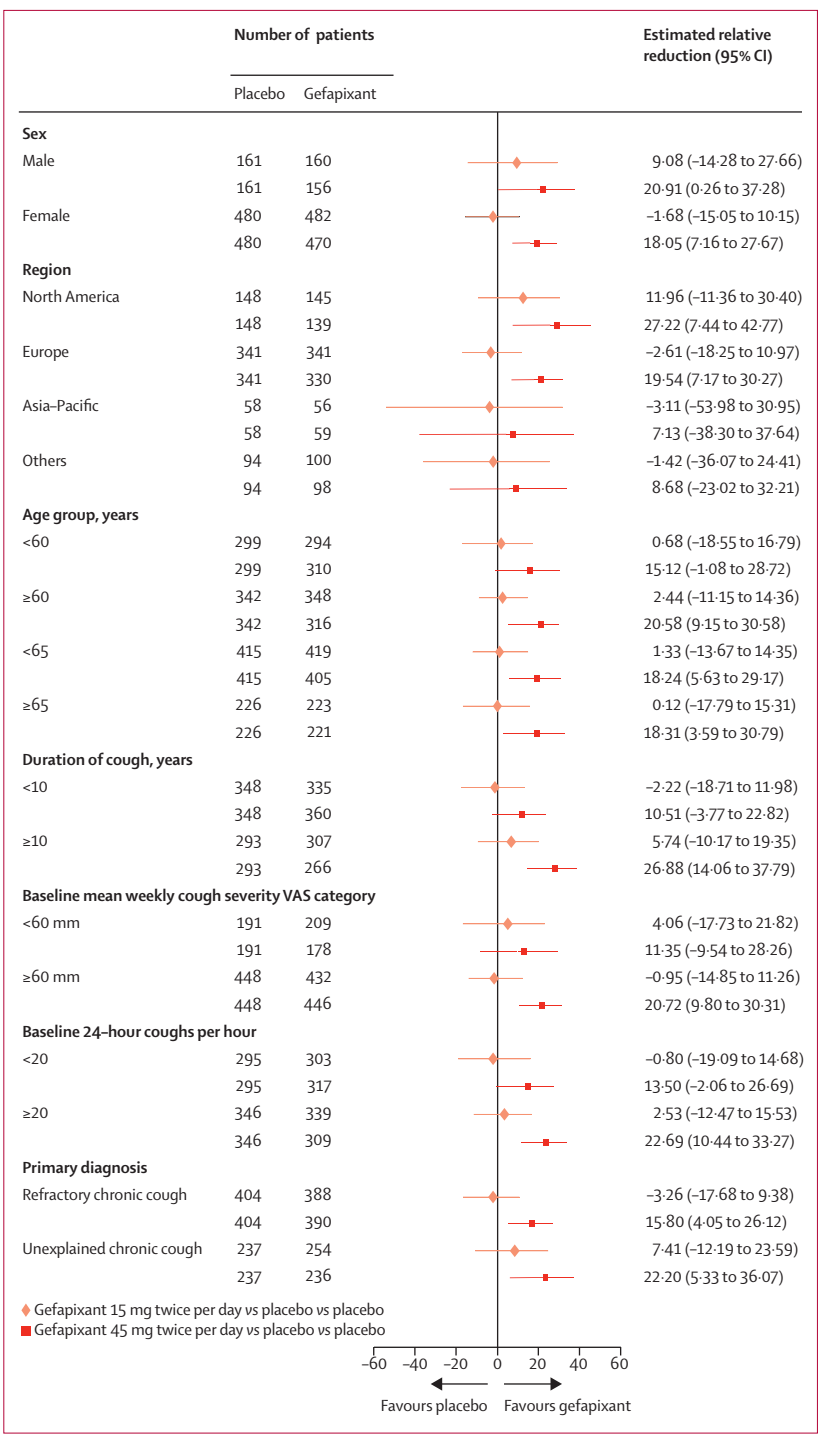


Figure 3: **Pooled* COUGH-1 and COUGH-2 (week 12) predefined subgroup analyses for 24-h cough frequency**

Error bars are 95% CIs. *Based on the Longitudinal Analysis of Covariance Model consisting of the change from baseline in log-transformed 24-h coughs per h at each post-baseline visit (up to week 12) as a response. The model includes trial, treatment, visit, treatment-by-visit interaction, sex, region, log-transformed baseline value, and log-transformed baseline value-by-visit as covariates. The unstructured covariance matrix is used to model the correlation among repeated measurements. The estimated relative reduction (relative to placebo) is calculated by 100 × (e^{DIFF} −1), in which DIFF is the treatment difference in change from baseline at week 12, as provided by the analysis of the log-transformed data. Additional statistical details are provided in the appendix (p 6), including information about sensitivity analyses regarding the potential effect of missing data. The subgroup analyses for 24-h cough frequency at the end of the main study periods of the individual trials are shown in the appendix (p 16).

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day	p value (gefapixant 45 mg twice per day *vs* placebo)
COUGH-1 (12-week main study period)				
Primary endpoint				
24-h cough frequency				
Number of patients with data	222	227	217	..
Baseline (geometric mean coughs per h)	22·8	19·9	18·2	..
Week 12 (geometric mean coughs per h)	10·3	9·7	7·1	..
Percentage of estimated relative reduction (95% CI) *vs* placebo	..	–1·56 (–22·99 to 16·13)	18·45 (0·86 to 32·92)	p=0·041
Key secondary endpoints*				
Awake cough frequency				
Number of patients with data	222	227	217	..
Baseline (geometric mean coughs per h)	30·4	25·8	24·1	..
Week 12 (geometric mean coughs per h)	13·4	12·6	9·1	..
Percentage of estimated relative reduction (95% CI) *vs* placebo	..	–2·95 (–25·19 to 15·33)	17·68 (–0·50 to 32·57)	Nominal p=0·056
Participants achieving 30% reduction in 24-h cough frequency at week 12				
Number of patients with data	222	227	217	..
Percentage of responders†	65·9%	66·2%	69·9%	..
Estimated OR *vs* placebo	..	1·01 (0·66 to 1·55)	1·2 (0·77 to 1·86)	Nominal p=0·42
Other secondary endpoints				
Leicester Cough Questionnaire (participants achieving ≥1·3-point change at week 12 from baseline for total score)				
Number of patients with data	217	226	214	..
Percentage of responders	61·3%	68·8%	67·3%	..
Estimated OR *vs* placebo	..	1·39 (0·92 to 2·12)	1·30 (0·85 to 1·98)	..
Cough severity VAS (participants achieving 30 mm improvement at week 12 from baseline)				
Number of patients with data	237	241	234	..
Percentage of responders	31·3%	36·7%	41·2%	..
Estimated OR *vs* placebo	..	1·27 (0·86 to 1·89)	1·54 (1·03 to 2·30)	..
Cough Severity Diary (participants achieving ≥1·3-point and ≥2·7-point reduction at week 12 from baseline)				
≥1·3-point reduction				
Number of patients with data	237	241	234	..
Percentage of responders	52·4%	62·1%	60·5%	..
Estimated OR *vs* placebo	..	1·48 (1·01 to 2·18)	1·39 (0·94 to 2·05)	..
≥2·7-point reduction				
Number of patients with data	237	241	234	..
Percentage of responders	28·6%	37·9%	40·1%	..
Estimated OR *vs* placebo	..	1·53 (1·01 to 2·30)	1·68 (1·11 to 2·54)	..
COUGH-2 (24-week main study period)				
Primary endpoint				
24-h cough frequency				
Number of patients with data	419	415	409	..
Baseline (geometric mean cough per h)	19·5	19·4	18·6	..
Week 24 cough frequency (geometric mean coughs per h)	8·3	8·1	6·8	..
Percentage of estimated relative reduction (95% CI) *vs* placebo	..	1·14 (–14·02 to 14·27)	14·64 (1·43 to 26·07)	p=0·031
Key secondary endpoints*				
Awake cough frequency				
Number of patients with data	419	415	409	..
Baseline (geometric mean coughs per h)	25·8	25·6	24·3	..
Week 24 (geometric mean coughs per h)	10·82	10·30	8·63	..
Percentage of estimated relative reduction (95% CI) *vs* placebo	..	3·03 (–12·12 to 16·14)	15·79 (2·50 to 27·27)	p=0·022

(Table 2 continues on next page)

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day	p value (gefapixant 45 mg twice per day *vs* placebo)
(Continued from previous page)				
Leicester Cough Questionnaire (participants achieving ≥1·3-point increase at week 24 from baseline for total score)				
Number of patients with data	406	404	399	..
Percentage of responders	70·1%	75·9%	76·8%	..
Estimated OR *vs* placebo	..	1·34 (0·97 to 1·85)	1·41 (1·02 to 1·96)	p=0·040
Participants achieving 30% reduction in 24-h cough frequency at week 24				
Number of patients with data	419	415	409	..
Percentage of responders†	66·9%	67·4%	72·9%	..
Estimated OR *vs* placebo	..	1·03 (0·75 to 1·40)	1·33 (0·96 to 1·83)	p=0·082
Other secondary endpoints				
Cough severity VAS (participants achieving 30 mm improvement at week 24 from baseline)				
Number of patients with data	428	426	425	..
Percentage of responders	40·9%	51·4%	53·3%	..
Estimated OR *vs* placebo	..	1·53 (1·14 to 2·05)	1·65 (1·23 to 2·22)	..
Cough Severity Diary (participants achieving ≥1·3-point and ≥2·7-point reduction at week 24 from baseline)				
≥1·3-point reduction				
Number of patients with data	428	426	425	..
Percentage of responders	69·1%	74·8%	77·1%	..
Estimated OR *vs* placebo	..	1·33 (0·96 to 1·83)	1·50 (1·08 to 2·09)	..
≥2·7 point reduction				
Number of patients with data	428	426	425	..
Percentage of responders	41·0%	46·6%	55·2%	..
Estimated OR *vs* placebo	..	1·25 (0·93 to 1·69)	1·77 (1·31 to 2·39)	..

OR=odds ratio. VAS=visual analogue scale. *Hypothesis testing was done and p values were calculated for key secondary endpoints in COUGH-2; p values for key secondary endpoints for COUGH-1 are nominal (ie, unadjusted) because of the multiplicity strategy (appendix pp 6–7). †Based on the logistic regression model. The covariates include treatment, visit, treatment-by-visit interaction, sex, region, baseline, and the interaction of baseline by visit.

Table 2: **Summary of efficacy endpoints**

these were 22 days (2–84) for placebo, 13 days (2–70) for gefapixant 15 mg twice per day, and 1 day (1–3) for gefapixant 45 mg twice per day in COUGH-1; and 34 days (IQR 2–72·5) for placebo, 12 days (2–47) for gefapixant 15 mg twice per day, and 2 days (1–5) for gefapixant 45 mg twice per in COUGH-2. Taste-related adverse events included ageusia (36 [4·9%] of 730 in COUGH-1 and 86 [6·5%] of 1314 in COUGH-2), dysgeusia (118 [16·2%] in COUGH-1 and 277 [20·1%] in COUGH-2), hypergeusia (three [0·4%] in COUGH-1 and two [0·5%] in COUGH-2), hypogeusia (19 [2·6%] in COUGH-1 and 80 [6·1%] in COUGH-2), and taste disorder (28 [3·8%] in COUGH-1 and 46 [3·5%] in COUGH-2). Dysgeusia—the most common taste adverse event across both studies—was often described as a metallic, bitter, or salty taste.

Serious adverse events over 52 weeks occurred in 44 (6·0%) of 730 participants in COUGH-1 and 74 (5·6%) of 1314 participants in COUGH-2 and were balanced between treatment groups. Three deaths were reported in COUGH-1: one death occurred while receiving gefapixant 15 mg twice per day after a respiratory tract infection and two deaths occurred while receiving placebo. Only one death was reported in COUGH-2 while receiving gefapixant 15 mg twice per day due to cardiopulmonary failure. None of the deaths were considered by the investigators to be related to the study medication (table 3).

Sensitivity analyses were done to explore any effect on efficacy outcomes from differential discontinuations between treatment groups due to taste-related adverse events. Results for sensitivity analyses are in the appendix (pp 14–15) and show minimal effect on the results from missing data.

Discussion

Findings from these two double-blind, randomised, placebo-controlled, phase 3 trials show that gefapixant was effective in the treatment of patients with refractory chronic cough or unexplained chronic cough. COUGH-1 confirmed reduction in objective cough frequency over 12 weeks with gefapixant 45 mg twice per day, a treatment duration that was previously assessed in a smaller phase 2b study;[20] COUGH-2 showed durability of cough frequency reduction over 24 weeks with gefapixant 45 mg twice per day. Importantly, the clinical relevance of the significant reductions in cough frequency was supported by the patient-reported key secondary

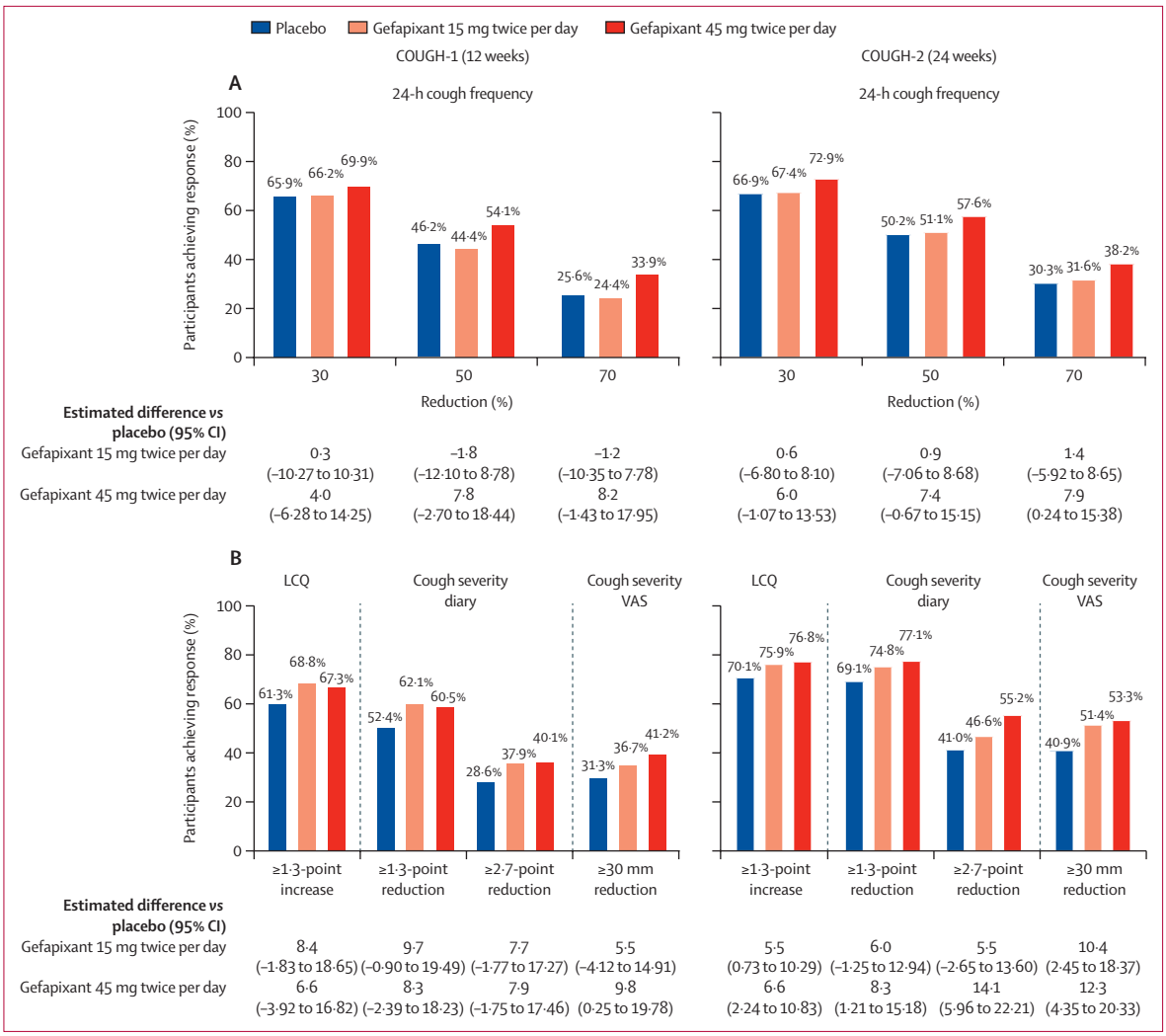


Figure 4: **Responder analyses for cough frequency and patient-reported outcome endpoints**
(A) 24-h cough frequency responders with 30% reduction, 50% reduction, and 70% reduction in coughs per h over 24 h. (B) Patient-reported outcome responders. LCQ=Leicester Cough Questionnaire. VAS=visual analogue scale.

efficacy outcome that showed that gefapixant 45 mg twice per day resulted in a greater proportion of participants achieving a clinically meaningful improvement in cough-specific quality of life as measured by a 1·3-point increase or more in the Leicester Cough Questionnaire. Improvements in cough frequency, severity, and cough-specific quality of life were observed from week 4, which were sustained throughout the treatment period in both studies. Although moderately increased benefits were evident for the 45 mg twice per day dose compared with placebo in the subgroup of patients with greater baseline cough severity, results were consistent with primary results for all subgroups assessed. The gefapixant 15 mg twice per day dose did not show a significant difference from placebo in the 24-h cough frequency in either trial. Adverse events over 52 weeks were largely due to mild or moderate taste disturbances and were more common in the gefapixant 45 mg twice per day group than in the other treatment groups. Serious adverse events were uncommon and equally distributed across treatment groups.

Both COUGH-1 and COUGH-2 provide—for the first time—large, well controlled, international, phase 3 trial evidence for treatment efficacy using validated measures of cough and cough-specific health-related quality of life in patients with refractory chronic cough or unexplained chronic cough. We recruited participants from more than 150 sites in a total of 26 countries, representing a large and globally diverse study population with demographics and cough characteristics consistent with previous descriptive reports of patients with chronic cough.[27] We did two phase 3 studies to evaluate whether the findings from one study could be replicated in the other;

the findings from COUGH-1 and COUGH-2 were consistent, demonstrating reproducibility of results in two large, global clinical trials. Additionally, the outcome measures and tools used to measure cough in these studies have been validated and shown to have a high level of reliability.[7,9,26,28–32]

Although participants receiving gefapixant 45 mg twice per day had improvements in cough symptoms, discontinuations due to adverse events and overall adverse events were driven by taste-related adverse events in this treatment group. We evaluated the effect of missing data due to higher discontinuations in the gefapixant 45 mg twice per day group; minimal effect was reported on results due to missing data as assessed by sensitivity analyses. These taste-related adverse events were generally mild or moderate, and were reversible with most participants achieving resolution either while on treatment or soon after discontinuation of treatment. The taste-related adverse events were also not associated with clinical sequalae (ie, weight loss, dehydration, or change in renal function). The heterotrimeric $P2X_{2/3}$ receptor is thought, based on animal studies, to be responsible for signalling between taste buds and gustatory sensory nerves, thus providing a plausible mechanism for the observations in these trials.[33] Serious adverse events were uncommon and occurred with similar incidence among treatment groups. Additionally, adverse events such as lower respiratory infections that would indicate a loss of protective cough were not observed to be different between active treatment groups and the placebo group, indicating that protective cough was not affected by treatment with gefapixant.[17]

Research in $P2X_3$ receptor antagonists for the treatment of chronic cough is ongoing with several agents including gefapixant. Clinical evidence with other $P2X_3$ receptor antagonists is limited to small studies of short duration.[34–36] Additional data with more selective and non-selective compounds might shed light on the consideration of $P2X_3$ homotrimer versus the $P2X_{2/3}$ heterotrimer with respect to efficacy and adverse events such as taste-related adverse events.

A notable issue in the study of treatments for chronic cough are large placebo responses. Placebo responses have been observed in other cough studies.[37,38] Although the reasons for these placebo responses are unclear, research has shown that cough is under voluntary control with both conscious and unconscious mechanisms.[38,39] Additionally, neurotransmitters such as endogenous opioids are thought to have a role in the placebo response observed in cough.[40] Importantly, higher brain centres process sensory information from the respiratory system and could potentially explain why placebo responses have been observed in other respiratory diseases such as allergic rhinitis and asthma.[41–43] Investigation of central brain activity during a cough challenge has shown phenomena such as reduction in capsaicin-induced brain activity and the urge to cough by placebo.[44] Although the biology of cough involves peripheral nerve fibres and the brain stem, substantial influence of higher brain circuits similar to other respiratory conditions also exists.[41,45] Therefore, a placebo response is expected in cough trials. In our study, we observed a particularly large placebo response in relation to previous studies in which placebo responses have been observed.[18,38,46] Although the change from baseline by 12 weeks with gefapixant 45 mg twice per day was consistent with a previous phase 2b study that showed a significant reduction in cough frequency for gefapixant 50 mg twice per day compared with placebo,[18] the placebo response was greater in

	Placebo	Gefapixant 15 mg twice per day	Gefapixant 45 mg twice per day
COUGH-1			
Number of participants	243	244	243
Any adverse event	184 (75·7%)	186 (76·2%)	208 (85·6%)
Serious adverse events	14 (5·8%)	17 (7·0%)	13 (5·3%)
Adverse events related to treatment*	47 (19·3%)	49 (20·1%)	158 (65·0%)
Adverse events of special interest			
Taste-related adverse events	11 (4·5%)	31 (12·7%)†	144 (59·3%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	0	3 (1·2%)	33 (13·6%)†
Back pain	19 (7·8%)	14 (5·7%)	20 (8·2%)
Dysgeusia	8 (3·3%)	22 (9·0%)‡	88 (36·2%)†
Headache	31 (12·8%)	34 (13·9%)	29 (11·9%)
Hypogeusia	1 (0·4%)	5 (2·0%)	13 (5·3%)†
Nasopharyngitis	51 (21·0%)	47 (19·3%)	50 (20·6%)
Taste disorder	2 (0·8%)	2 (0·8%)	24 (9·9%)†
COUGH-2			
Number of participants	432	442	440
Any adverse event	349 (80·8%)	373 (84·4%)	399 (90·7%)
Serious adverse events	25 (5·8%)	24 (5·4%)	25 (5·7%)
Adverse events related to treatment*	91 (21·1%)	145 (32·8%)	312 (70·9%)
Adverse events of special interest			
Taste-related adverse events	36 (8·3%)	89 (20·1%)†	303 (68·9%)†
Most common adverse events (>8% in a single treatment group)			
Ageusia	6 (1·4%)	13 (2·9%)	67 (15·2%)†
Dysgeusia	28 (6·5%)	56 (12·7%)‡	193 (43·9%)†
Headache	67 (15·5%)	74 (16·7%)	70 (15·9%)
Hypogeusia	3 (0·7%)	17 (3·8%)‡	60 (13·6%)†
Influenza	35 (8·1%)	30 (6·8%)	24 (5·5%)
Nasopharyngitis	70 (16·2%)	93 (21·0%)	70 (15·9%)
Nausea	32 (7·4%)	26 (5·9%)	47 (10·7%)
Taste disorder	1 (0·2%)	8 (1·8%)‡	37 (8·4%)†
Upper respiratory tract infection	27 (6·3%)	38 (8·6%)	30 (6·8%)

Data are n or n (%). Difference in percentage versus placebo for taste-related adverse events were tested for significance. Taste-related adverse events included ageusia, dysgeusia, hypergeusia, hypogeusia, and taste disorder; dysgeusia is defined as a change in taste to something specific, such as salty or sweet, taste disorder is defined as a non-specific change in taste, ageusia is defined as loss of taste, hypergeusia is defined as increased taste, and hypogeusia is defined as diminished taste. *Determined to be possibly, probably, or definitely related to study treatment by the investigator. †p≤0·001. ‡p≤0·05.

Table 3: **Summary of adverse events by 52 weeks in COUGH-1 and COUGH-2**

COUGH-1 and COUGH-2 leading to a smaller relative reduction compared with placebo. However, these studies are the first global, phase 3 trials to be done in patients with chronic cough; therefore, no benchmark exists for a standard placebo response to expect in this population. Nevertheless, gefapixant 45 mg twice per day showed significant reductions in cough frequency in each trial, relative to the reductions seen with those receiving placebo accompanied by clinically meaningful improvement in patient-reported cough-specific quality of life. The effects seen with gefapixant in refractory chronic cough and unexplained chronic cough have been consistent and reproducible across five randomised controlled trials.

For the **data sharing policy** see http://engagezone.msd.com/ds_documentation.php

Both studies have limitations. The large placebo response in these studies presented limitations with regard to reduced placebo-adjusted effect sizes and in doing statistical testing of secondary endpoints in COUGH-1 because of the multiplicity strategy. Another limitation was that an active comparator was not included in these trials because of the absence of licensed medications for refractory chronic cough or unexplained chronic cough.

In summary, COUGH-1 and COUGH-2, the first-ever phase 3 trials of a novel treatment specifically for refractory chronic cough and unexplained chronic cough, have shown that gefapixant 45 mg twice per day is an effective therapeutic option to address the current absence of licensed treatments for patients with refractory chronic cough and unexplained chronic cough. Adverse events reported were mild or moderate in severity and most commonly related to taste.

Contributors

LPM, SSB, AHM, PVD, IDP, JS, BI, SAG, DRM, and JAS conceived, designed, and planned this study. LPM, SSB, AHM, SAG, and JAS collected and acquired the data. AHM, PVD, IDP, QL, AT, CLR, DRM, and JAS analysed the data. LPM, SSB, AHM, PVD, IDP, JS, AMN, QL, AT, CLR, DRM, and JAS interpreted the data. LPM, AHM, IDP, JS, DRM, and JAS drafted the manuscript. All authors critically reviewed the manuscript. LPM, JS, AMN, QL, AT, BI, SAG, CLR, DRM, and JAS revised the manuscript. All authors had access to all the data in the study. All authors were responsible for the decision to submit for publication.

Declaration of interests

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Data sharing

Merck Sharp & Dohme's, a subsidiary of Merck & Co, data sharing policy, including restrictions, is available online. Requests for access to the clinical study data can be submitted through the EngageZone website or via email to dataaccess@merck.com

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