Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial

*Jaclyn A Smith, Michael M Kitt, Alyn H Morice, Surinder S Birring, Lorcan P McGarvey, Mandel R Sher, Yu-Ping Li, Wen-Chi Wu, Zhi Jin Xu, David R Muccino, Anthony P Ford, on behalf of the Protocol 012 Investigators**

Summary

Background Gefapixant is a P2X3 receptor antagonist that has shown promise for the treatment of refractory and unexplained chronic cough. The aim of this study was to evaluate the efficacy of gefapixant compared with placebo after 12 weeks of treatment for refractory chronic cough or unexplained chronic cough.

Methods We did a 12-week, phase 2b, randomised, double-blind, placebo-controlled study in patients with refractory chronic cough or unexplained chronic cough aged 18–80 years who were recruited from 44 primarily outpatient pulmonologist or allergist sites in the UK and the USA. Eligible patients had refractory or unexplained chronic cough lasting 1 year or longer, no radiographic chest abnormality, and 40 mm or more on a 100-mm cough severity visual analogue scale at enrolment. Patients were randomly assigned to receive placebo or one of three doses (7·5 mg, 20 mg, or 50 mg) of oral gefapixant twice daily, every day, for 84 days; visits to investigative sites were on days 1, 28, 42, 56, 70, 84, and 85. The randomisation schedule was computer generated using a permuted block algorithm by Advance Research Associates (Santa Clara, CA, USA). Patients and all personnel involved in the conduct and interpretation of the study were masked to treatment assignment. The primary endpoint was placebo-adjusted change from baseline in awake cough frequency after 12 weeks, assessed in the full analysis set, which is a subset of the intention-to-treat population. Adverse events were monitored and safety was evaluated in all patients receiving one or more doses of study drug. This trial is registered with ClinicalTrials.gov, NCT02612610.

Findings Between Dec 21, 2015, and July 26, 2016, 253 patients were randomly assigned to placebo (n=63), gefapixant 7·5 mg (n=64), gefapixant 20 mg (n=63), or gefapixant 50 mg (n=63) twice daily. The mean age of patients was 60·2 (SD 9·9) years and 193 (76%) were women. At 12 weeks, patients' geometric mean awake cough frequency was 18·2 coughs per h (geometric SD 3·1) with placebo, and 14·5 coughs per h (3·7) with 7·5 mg, 12·0 coughs per h (4·2) with 20 mg, and 11·3 coughs per h (2·8) with 50 mg gefapixant. Estimated percentage change relative to placebo was –22·0% (–41·8 to 4·6; p=0·097) with 7·5 mg, –22·2% (–42·0 to 4·3; p=0·093) with 20 mg, and –37·0% (95% CI –53·3 to –14·9; p=0·0027) with 50 mg gefapixant. Dysgeusia was the most common adverse event, occurring in three (5%) patients given placebo, six (10%) given 7·5 mg gefapixant, 21 (33%) given 20 mg gefapixant, and 30 (48%) given 50 mg gefapixant.

Interpretation Targeting purinergic receptor P2X3 with gefapixant at a dose of 50 mg twice daily significantly reduced cough frequency in patients with refractory chronic cough or unexplained chronic cough after 12 weeks of treatment compared with placebo. Further development of gefapixant is warranted for the treatment of chronic cough.

Funding Afferent Pharmaceuticals (acquired by Merck & Co., Inc., Kenilworth, NJ, USA).

Lancet Respir Med 2020; 8: 775–85

Published Online February 25, 2020 https://doi.org/10.1016/S2213-2600(19)30471-0

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*Investigators are listed in the appendix

Division of Infection, Immunity, and Respiratory Medicine, University of Manchester, Manchester, UK (Prof J A Smith PhD); **Manchester University NHS Foundation Trust, Manchester, UK** (Prof J A Smith); **Merck & Co., Kenilworth, NJ, USA** (M M Kitt MD, Z J Xu PhD, D R Muccino MD, A P Ford PhD, W-C Wu PhD); **Hull York Medical School, Cottingham, UK** (A H Morice MD); **Centre for Human & Applied Physiological Sciences, School of Basic & Medical Biosciences, Faculty of Life Sciences & Medicine, King's College London, London, UK** (Prof S S Birring MD); **Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK** (Prof L P McGarvey MD); **Center for Cough, Largo, FL, USA** (Prof M R Sher MD); **and GetStat Solutions, LLC, Palo Alto, CA, USA** (Y-P Li PhD)

Correspondence to: Prof Jaclyn Smith, Division of Infection, Immunity and Respiratory Medicine, Education and Research Centre, University of Manchester, Manchester M23 9LT, UK **jacky.smith@manchester.ac.uk**

See Online for appendix

Introduction

Epidemiological studies indicate that chronic cough (ie, a cough lasting >8 weeks) affects 4–10% of adults worldwide.[1,2] However, no effective licensed therapies exist for this problem. Individuals reporting chronic cough who have never smoked are likely to be older, be female, have abdominal obesity, have occupational exposure to dust or fumes, or be diagnosed with conditions such as asthma, gastro-oesophageal reflux disease, upper airway cough syndrome, or bronchiectasis.[1] Nonetheless, among patients diagnosed with these conditions, most do not complain of chronic coughing, which suggests that a distinct pathophysiological process underlies the symptomatic trait of chronic cough.

Although patients with chronic cough can benefit from the treatment of associated conditions—most commonly asthma, gastro-oesophageal reflux disease, and upper airways cough syndrome—it is increasingly recognised that cough does not improve with such treatments in many patients; these patients are often classified as having refractory chronic cough. A minority of patients with chronic cough have no evidence of any underlying condition and can be considered to have unexplained chronic cough. Unfortunately, there are no data estimating

Research in context

Evidence before this study

Chronic cough affects 4–10% of the general population, a proportion of whom have a cough that does not resolve with treatment for suspected associated conditions or no known cause of chronic cough. Hyperexcitability of neuronal pathways mediating cough might be a therapeutic target for patients with a refractory or unexplained condition. We searched PubMed with the terms "P2X3" and "chronic cough". We had no restrictions on article type, language, or date of publication. We found 21 manuscripts. A previous study of gefapixant, a P2X3 receptor antagonist, at a supratherapeutic dose of 600 mg showed a significant reduction in cough frequency compared with placebo in patients with refractory chronic cough.

Added value of this study

We report the results from the largest trial of gefapixant to date in patients with chronic cough. We evaluated lower doses of gefapixant within a therapeutic dose range and over a longer (12 week) treatment period than any previous trials, and found significant reductions in cough frequency in patients who received a 50 mg dose of gefapixant.

Implications of all the available evidence

Our results confirm the therapeutic potential of targeting P2X3 receptors for a clinically meaningful reduction of chronic cough. The evidence from this trial supports further development of gefapixant. Phase 3 studies evaluating gefapixant are ongoing (NCT03449134 and NCT03449147) and will further evaluate efficacy and tolerability of this novel mechanism.

the proportion of patients with chronic cough who have refractory chronic cough or unexplained chronic cough. Cough hypersensitivity syndrome is a diagnosis that might be applicable to refractory chronic cough and unexplained chronic cough; this syndrome has been attributed, hypothetically, to disordered sensory neural function.[3] Although few treatment options exist, hyperexcitability of neuronal pathways mediating cough might be a therapeutic target and, indeed, there is some evidence that patients with refractory chronic cough can respond to therapies that modulate neuronal function (eg, morphine, gabapentin, and amitriptyline) and behavioural interventions.[4–6]

Purinergic receptor P2X3 is an ATP-gated ion channel found predominantly on peripheral sensory nerves and known to be expressed by fibres innervating the airways.[7] A small proof-of-concept study[8] in patients with refractory chronic cough showed that a 2-week treatment with high-dose (600 mg twice daily) gefapixant (MK-7264; previously known as AF-219), a P2X3 receptor antagonist, reduced objective cough frequency by 75% when adjusted for placebo effects (95% CI 50–88; p=0·0003). Subsequent studies suggested that maximum efficacy was retained at doses as low as 50 mg twice daily, with an improved tolerability profile.[9,10] The aim of this randomised controlled trial was to evaluate the effectiveness of three doses of gefapixant (7·5 mg, 20 mg, and 50 mg twice daily) compared with placebo, after 12 weeks of treatment, in reducing cough frequency during waking hours in patients with refractory chronic cough or unexplained chronic cough.

Methods

Study design and participants

This 12-week, phase 2b, randomised, double-blind, placebo-controlled, parallel-group study was done in 44 centres in the UK and USA. Adults aged 18–80 years who marked cough severity at 40 mm or higher on a 100-mm cough severity visual analogue scale at the screening visit were eligible.

We enrolled patients who had refractory chronic cough or unexplained chronic cough lasting 1 year or longer, according to the American College of Chest Physicians (ACCP) and the British Thoracic Society guidelines,[11,12] with no substantial abnormalities on a chest x-ray contributing to cough within the past 5 years (chest radiology within 5 years was permitted to avoid repeated exposure to radiation from radiographic scans done to find an underlying cause of cough in this patient population).

Patients were excluded if they were current smokers, had quit smoking within 6 months of enrolment in the study, had a ratio of forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of less than 60%, had used opioids within 1 week of the study, or had initiated treatment with an angiotensin-converting enzyme (ACE) inhibitor or had an upper or lower respiratory tract infection within 4 weeks of the study. Guidelines suggest discontinuation of ACE inhibitors if they are the cause of cough; in our study, stable ACE inhibitor therapy was permitted if it was determined that the treatment was not the cause of the patient's cough. A complete list of the inclusion and exclusion criteria and previous medical history of participants at baseline are provided in the appendix (p 10).

Patients gave written informed consent before enrolment. The study was approved by the Investigational Review Boards or Ethics Review Committees of the 44 study centres in the UK and USA, and done in accordance with the principles of Good Clinical Practice.

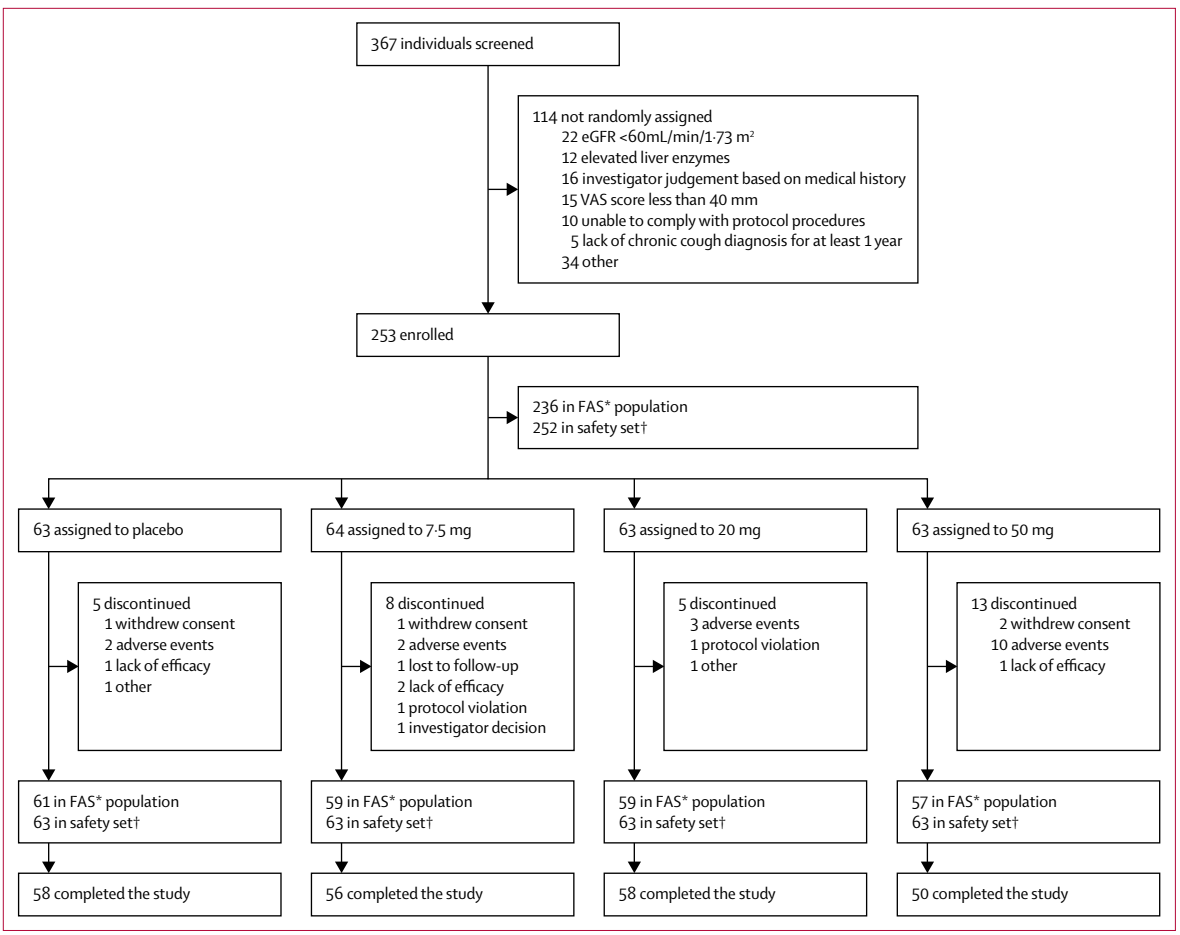

Figure 1: **Trial profile**
*FAS population is the full analysis set, which included all randomly assigned patients who had taken at least one dose of study medication and provided at least one baseline and one post-baseline primary endpoint observation during the treatment period. †Safety set is defined as all patients who were randomly assigned and received any amount of study treatment.

Randomisation and masking

Patients were randomly assigned in a 1:1:1:1 ratio to gefapixant 7·5 mg twice daily, gefapixant 20 mg twice daily, gefapixant 50 mg twice daily, or a matching placebo twice daily. The randomisation was stratified by country and was done by a centralised interactive voice or web response system. The randomisation schedule was computer generated, using a permuted block algorithm, and allocated randomisation numbers to patients. Randomisation schedules were generated by Advance Research Associates (Santa Clara, CA, USA) and allocation was done by Endpoint (San Francisco, CA, USA). A two-stage randomisation was used. Patients were first randomly assigned to one of the dose groups using a balanced 1:1:1 (group one was gefapixant 7·5 mg or matched placebo, group two was gefapixant 20 mg or matched placebo, and group three was gefapixant 50 mg or matched placebo) randomisation. After being randomly assigned to their dose group, individuals were assigned to treatment using an unbalanced 3:1 (gefapixant to placebo) randomisation.

This study used a double-masking design in which patients and all personnel involved with the conduct and the interpretation of the study, including the investigators, investigational site personnel, contract research organisation personnel, home health nurses, cough analysts at VitaloJAK (Vitalograph, Buckingham, UK), and sponsor staff were masked to the treatment codes. Randomisation data were kept stictly confidential, filed securely at Merck & Co., Inc. (Kenilworth, NJ, USA) or Endpoint (San Francisco, CA, USA), and were accessible only to authorised persons 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

Patients were screened during a 2-week period. On day 0, patients had baseline assessments; on the morning of day 1, they received the first dose of study drug (oral

	Placebo (n=63)	Gefapixant			Total (n=253)
		7·5 mg (n=64)	20 mg (n=63)	50 mg (n=63)	
Sex					
Female	47 (75%)	48 (75%)	48 (76%)	50 (79%)	193 (76%)
Male	16 (25%)	16 (25%)	15 (24%)	13 (21%)	60 (24%)
Age, years					
Mean age, years (SD)	60·0 (10·9)	59·9 (10·5)	61·8 (9·1)	59·3 (9·2)	60·2 (9·9)
Median (range)	61·0 (23–76)	61·5 (22–78)	63·0 (40–79)	60·0 (36–77)	61·0 (22–79)
Race					
White	59 (94%)	60 (94%)	60 (95%)	55 (87%)	234 (92%)
Other*	4 (6%)	4 (6%)	3 (5%)	8 (13%)	19 (8%)
Body-mass index, kg/m²					
Mean (SD)	27·6 (4·8)	27·9 (4·5)	28·0 (4·6)	27·2 (5·0)	27·7 (4·7)
Median	27·3	27·6	27·7	26·7	27·4
FEV_1:FVC ratio, %					
Mean (SD)	83·5% (12·4)	82·2% (13·3)	80·2% (11·1)	80·9% (11·8)	81·7% (12·2)
Median	82%	80%	78%	80%	80%
Duration of cough, years					
Mean (SD)	17·1 (13·3)	13·5 (10·0)	14·9 (13·9)	12·3 (8·2)	14·5 (11·7)
Median	12·0	12·0	8·0	11·0	11·0
Country					
USA	42 (67%)	41 (64%)	41 (65%)	41 (65%)	165 (65%)
UK	21 (33%)	23 (36%)	22 (35%)	22 (35%)	88 (35%)
Smoking status					
Never smoked	45 (71%)	49 (77%)	35 (56%)	48 (76%)	177 (70%)
Former smoker	18 (29%)	15 (23%)	28 (44%)	15 (24%)	76 (30%)

FEV_1=forced expiratory volume at 1 s. FVC=forced vital capacity. *Includes black, African American, Native American, Native Alaskan, Asian, Pacific Islander, or mixed race.

Table 1: **Baseline patient characteristics**

gefapixant 7·5 mg twice daily, oral gefapixant 20 mg twice daily, oral gefapixant 50 mg twice daily, or a matching placebo), which was administered in the clinic. Subsequent treatment visits were scheduled for days 28, 42, 56, 70, 84, and 85, with follow-up visits on days 98 and 99.

Objective cough frequency was captured with 24-h sound recordings at baseline and on days 28, 56, 84, and 98 using VitaloJAK (Vitalograph), an acoustic recording device. Sound recordings were filtered by custom-written software to remove most non-cough sounds. Individual explosive cough sounds were then counted by trained analysts who reviewed the filtered recordings both visually and audibly in custom-written software (Vitalograph).[13]

Subjective assessments of cough severity were made by patients using a 100-mm visual analogue scale at screening, baseline, and on days 28, 56, 84, 85, 98, and 99. Although the cough severity visual analogue scale has not been formally validated, it has been widely used in studies of novel therapies for chronic cough, results obtained with the scale correlate with those from other cough measures, and measurements have been shown to be highly responsive to change.[17,18] Patient-reported daily cough scores and a cough severity diary (comprising seven items with three subscales: cough frequency, intensity, and disruption)—with scores from 0 (best) to ten (worst)—were recorded at screening, baseline, daily throughout the treatment period, and at follow-up. Patients completed a Leicester Cough Questionnaire, a measure of health-related quality of life,[14] at baseline and on days 28, 56, and 85. The Leicester Cough Questionnaire has been validated previously in patients with chronic cough,[14] and the cough severity diary and daily cough score have undergone some initial testing.[15,16]

Outcomes

The primary efficacy endpoint was change from baseline in awake objective cough frequency at each dose studied after 12 weeks (day 84) of treatment. Secondary endpoints were change in awake objective cough frequency after 4 weeks (day 28) and 8 weeks (day 56) of treatment; change in 24-h objective cough frequency and sleep objective cough frequency after 4 weeks (day 28), 8 weeks (day 56), and 12 weeks (day 84) of treatment; change in awake objective cough frequency at the follow-up visit (14 weeks; day 98); change from baseline in severity measures on the cough severity visual analogue scale; change from baseline in cough-specific quality-of-life assessed using the Leicester Cough Questionnaire (individual domain and total scores); and awake and 24-h cough frequency responder endpoints (ie, ≥70% reduction, ≥50% reduction, and ≥30% reduction). Other secondary outcomes included Patient's Global Impression of Change and Clinician's Global Impression of Change.

Vital signs, laboratory assessments, and adverse events were checked at each visit. Adverse events were assessed by medical staff at the study sites for their seriousness and relationship to study medication. Urinalysis and estimated glomerular filtration rate were done at screening and at all treatment visits. Paraesthesia, hypoaesthesia, and dysgeusia were adverse events of special interest and were queried further for frequency, severity, and duration using a structured taste questionnaire. An acceptability questionnaire completed at the end of treatment asked patients, "How likely would you be to take this medication?" across the time-frames of twice daily, 4 weeks or longer, 6 months or longer, or 1 year or longer.

Statistical analysis

The primary hypothesis was that one dose or more of gefapixant would be superior to placebo for the mean change from baseline in awake cough frequency (on the natural log scale) at 12 weeks. Assuming a dropout rate of 13%, approximately 200 patients were to be randomly assigned (≥43 evaluable patients in each treatment group), providing 85% power to detect a difference of 25 or more coughs per h for gefapixant versus placebo for the primary endpoint. This assumed a standard

deviation for the change from baseline of 38 using a Student's *t* test (two-sided, significance level of 0·05). The sample size estimates were based on a previous study of gefapixant.[9,10]

The primary efficacy endpoint was analysed using a mixed model repeated measures analysis and the baseline value (on the natural log scale) was included as a covariate; this was done on the full analysis set, which was a subset of the intention-to-treat population. The treatment group means relative to placebo were compared at day 84. Type I error rate for the primary efficacy testing was controlled by sequential comparisons of gefapixant versus placebo from a dose of 50 mg to 20 mg and finally to 7·5 mg.

The full analysis set (subset to the intention-to-treat population), which included all randomly assigned patients who had taken at least one dose of study medication and provided at least one baseline and one post-baseline primary endpoint observation, was used to evaluate efficacy. The per-protocol set was used to confirm efficacy parameters; the per-protocol set was defined as all patients in the full analysis set who did not have major protocol deviations, which are reviewed or determined before the database lock and unblinding; took study drug on at least 80% of compliance from the first to the last day of study treatment; and had a baseline awake cough frequency of five or more. The safety analysis set, which included all randomly assigned patients who had received at least one dose of study drug, was used to evaluate safety and tolerability. Of note, the p values for secondary efficacy variables in this study have not been adjusted for multiple comparisons.

Missing data were assumed to be missing at random for the primary analyses using a mixed model with repeated measures (missing data for other efficacy and safety endpoints were not imputed). This type of model accounts only for non-missing values, which means that the probability of a value being missing, conditional on the observed data and factors in the statistical model, is random and not dependent on the unknown value of the missing datapoint. The assumption that missing data were missing at random was assessed with missing data sensitivity analyses under missingness not at random to evaluate the robustness of efficacy results and the effect of missing data. Details are available in the appendix (p 6). This trial is registered with ClinicalTrials.gov, NCT02612610.

	Placebo (n=61)	Gefapixant		
		7·5 mg (n=59)	20 mg (n=59)	50 mg (n=57)
Geometric mean awake cough frequency				
Baseline, coughs per h (GSD)*	27·6 (2·3)	27·4 (2·7)	24·1 (3·0)	28·8 (2·2)
Week 4, coughs per h (GSD)*	17·7 (2·7)	14·2 (3·5)	14·4 (3·4)	11·8 (3·1)
Week 4 estimated change† relative to placebo, % (95% CI; p value)	..	–19·0% (–39·1 to –7·7; p=0·15)	–7·5% (30·3 to 22·7); p=0·59	–39·0% (–54·2 to 18·7; p=0·0008)
Week 8, coughs per h (GSD))*	19·5 (2·4)	12·9 (3·9)	12·5 (4·3)	10·7 (3·1)
Week 8 estimated change relative to placebo, % (95% CI; p value)	..	–32·0% (–50·6 to –6·6; p=0·0177)	–27·2% (–46·9 to 0·0; p=0·0498)	–44·8% (–60·1 to –23·6; p=0·0004)
Week 12, coughs per h (GSD)*	18·2 (3·1)	14·5 (3·7)	12·0 (4·2)	11·3 (2·8)
Week 12 estimated change relative to placebo, % (95% CI; p value)‡	..	–22·0% (–41·8 to 4·6; p=0·097)	–22·2% (–42·0 to 4·3; p=0·093)	–37·0% (–53·3 to –14·9; p=0·0027)
Geometric mean 24-h cough frequency				
Baseline, coughs per h (GSD)*	20·5 (2·2)	20·0 (2·7)	17·6 (3·0)	21·9 (2·2)
Week 4, coughs per h (GSD)*	13·1 (2·7)	10·5 (3·4)	10·8 (3·3)	8·7 (3·2)
Week 4 estimated change relative to placebo, % (95% CI; p value)	..	–17·0% (–37·3 to 9·8; p=0·19)	–5·1% (–28·1 to 25·2; p=0·71)	–40·6% (–55·2 to –21·4; p=0·0003)
Week 8, coughs per h (GSD)*	14·5 (2·3)	9·2 (3·9)	9·5 (4·1)	7·9 (3·2)
Week 8 estimated change relative to placebo, % (95% CI; p value)	..	–33·1% (–50·7 to –9·3; p=0·0099)	–24·5% (–44·2 to 2·3; p=0·07)	–46·0% (–60·4 to –26·4; p=0·0001)
Week 12, coughs per h (GSD)*	13·7 (2·9)	10·8 (3·6)	8·8 (4·1)	8·5 (2·8)
Week 12 estimated change relative to placebo, % (95% CI; p value)	..	–21·0% (–40·3 to 4·6; p=0·10)	–22·1% (–41·1 to 3·2; p=0·08)	–37·6% (–53·1 to –16·9; p=0·0014)

GSD=geometric SD. *Unadjusted data. † Change from baseline was based on mixed model repeated measures analysis in the full analysis set. ‡Primary efficacy endpoint.

Table 2: **Objective measurements of cough frequency in the full analysis set**

Protocol amendment

The protocol was amended on March 7, 2016, to allow the inclusion of patients with unexplained chronic cough (ie, to clarify that in addition to patients with cough refractory to identified associated causes, those with no apparent associated cause should be included in the study). This is an important group of patients with chronic cough who might benefit from treatment with a P2X3 receptor antagonist. Additionally, stable doses of opioids in patients who continued to experience troublesome cough and who required opioids for other indications were permitted, whereas the following medications were added to the prohibited list because these could confound the study results: pregabalin, gabapentin, thalidomide, or amitriptyline, and chlorpheniramine maleate extended-release tablets. The primary efficacy endpoint was changed on Dec 16, 2015, to include the week 4 timepoint to characterise the efficacy profile of gefapixant at early time points, but was subsequently removed on Nov 28, 2016, to avoid complicating the analysis of results due to multiple primary endpoints.

Role of the funding source

Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, sponsored this study. Academic advisors and representatives of the sponsor 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 sponsor. The sponsor provided results and

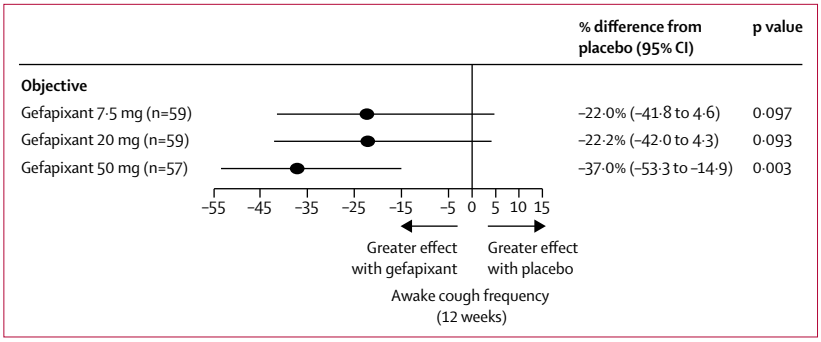

Figure 2: **Forest plot of change in awake cough frequency with gefapixant versus placebo in the full analysis set**

Data were assessed using a mixed model repeated measures analysis that included fixed effects for treatment group, visit, country, and treatment-by-visit interaction, and the baseline value as a covariate. The analysis of change from baseline in awake objective cough frequency and 24-hour objective cough frequency was based on log-transformed data.

methodological details. All the authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

Results

This trial was initiated on Dec 21, 2015, and completed on Nov 4, 2016. Between Dec 21, 2015 and July 26, 2016, we screened 367 individuals, of whom 253 patients were enrolled and randomly assigned to gefapixant 7·5 mg (n=64 patients), 20 mg (n=63), or 50 mg (n=63), or a matching placebo (n=63) twice daily (figure 1). 193 (76%) were women, 234 (92%) were white, and the mean age was 60·2 (SD 9·9) years (table 1). The mean duration of cough for the whole population was 14·5 (SD 11·7) years. The FEV_1:FVC ratio was normal (>80%) and most patients had never smoked (table 1). A summary of patients' medical history at baseline is provided in the appendix (p 10). At baseline, the geometric mean number of coughs per h while awake was 27·6 (median 31·7) with placebo, 27·4 (27·5) with 7·5 mg gefapixant, 24·1 (28·2) with 20 mg gefapixant, and 28·8 (28·0) with 50 mg gefapixant. Mean measurement at baseline on the cough severity visual analogue scale was 57·4 mm (SD 23·1) with placebo, 56·7 mm (20·7) with 7·5 mg gefapixant, 58·3 mm (25·1) with 20 mg gefapixant, and 57·9 mm (19·7) with 50 mg gefapixant.

Of the 253 randomly assigned patients, 252 (one patient was randomly assigned but not treated) took at least one dose of study medication or placebo and were included in the safety analysis set. 236 patients took at least one dose of study medication or placebo, provided one or more baseline and one or more post-baseline primary endpoint observations, and were included in the full analysis set. 222 patients completed the study, with adverse events reported as the most common reason for discontinuation (figure 1).

Gefapixant 50 mg showed a significant reduction in awake objective cough frequency after 12 weeks compared with placebo; the percentage reduction relative to placebo was –37·0% (95% CI –53·3 to –14·9; p=0·0027), a reduction from baseline of 57·6% (47·2–65·9; table 2).

The percentage reductions from baseline in awake objective cough frequency after 12 weeks for the 7·5 mg and 20 mg doses of gefapixant were greater than that of placebo, but the relative differences (–22·0%, 95% CI –41·8 to 4·6% [p=0·097] and –22·2%, –42·0 to 4·3 [p=0·093], respectively) were not significant (table 2, figures 2 and 3). Sensitivity analyses suggested that these results were robust to the effects of missing data (appendix p 11). A subgroup analysis was done to evaluate the effect of duration of cough on efficacy outcomes, considering the long mean duration of cough observed at screening; subgroup analyses did not suggest a significant effect of duration on efficacy outcomes, although patients with a shorter duration (<10 years) showed a higher reduction in cough frequency (appendix p 12). At week 14 (day 98; 2 weeks after the last dose of gefapixant), the mean (SD) change from week 12 in awake objective cough frequency (coughs per h) was 7·0 (18·5) with 50 mg gefapixant, 5·1 (18·2) with 20 mg gefapixant, 1·4 (29·2) with 7·5 mg gefapixant, and 1·2 (21·4) with placebo (figure 3). Patients who had received gefapixant remained below baseline and thus did not show evidence of a rebound effect (appendix p 13).

A prespecified responder analysis in Awake Cough Frequency at week 12 showed that 80% of patients who received gefapixant 50 mg had a 30% reduction compared with 44% who received placebo; among those with a 50% reduction of cough frequency were 51% of patients who received gefapixant 50 mg compared with 25% who received placebo and 31% of patients who received gefapixant 50 mg had a 70% or greater reduction compared with 16% who received placebo (appendix p 7).

Results for the secondary objectives and patient-reported endpoints supported the efficacy of gefapixant 50 mg and its superiority over placebo (tables 2 and 3); p values for secondary efficacy variables are nominal, because no adjustment was made for multiplicity. At 8 weeks, awake cough frequency was lower in patients receiving 7·5 mg gefapixant or 20 mg gefapixant than in those taking placebo, and 24-hour cough frequency was lower in patients receiving the 7·5 mg dose (table 2). Cough frequency during sleep was low and changes from baseline between treatment groups were not significant (appendix p 14). Patients receiving gefapixant showed improvements on the cough severity visual analogue scale after 12 weeks, with the greatest change from baseline for gefapixant 50 mg (table 3, figure 3). At week 12, the mean daily cough severity diary score (relative to placebo) reduced by –0·4 (95% CI –1·0 to 0·3; nominal p=0·25) in the gefapixant 7·5 mg group, by –0·6 (–1·2 to 0·0; nominal p=0·07) in the 20 mg group, and by –0·7 (–1·4 to –0·1; nominal p=0·0197) in the 50 mg group. Reductions in the daily cough score at 12 weeks were greater for patients taking

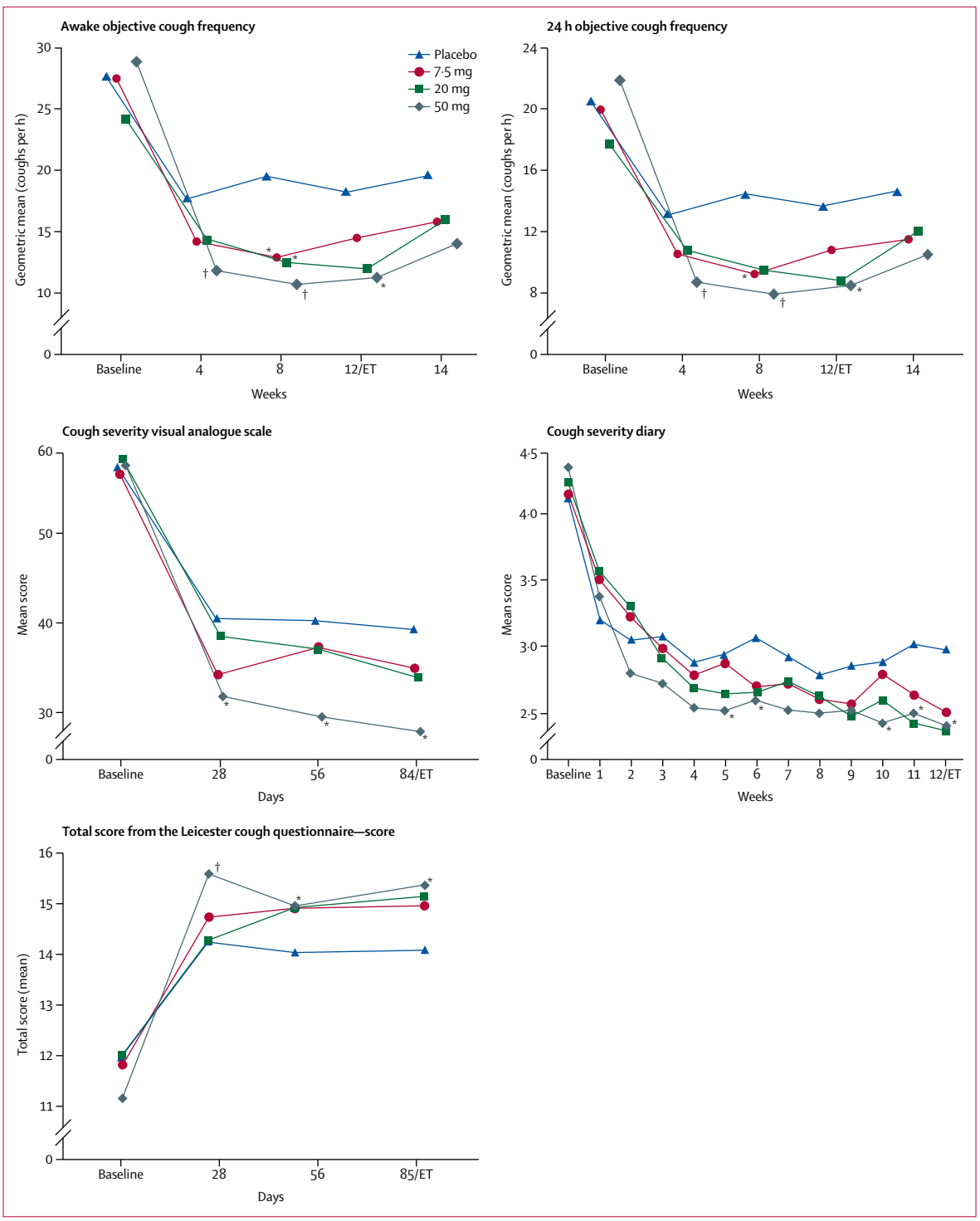

Figure 3: **Efficacy measurements over time for gefapixant versus placebo in the full analysis set**
Statistical testing was not done at week 14. ET=end of treatment. *p<0·001. †p<0·05.

gefapixant than for patients who received placebo (nominal p values >0.05; table 3). Weekly changes in cough severity diary are shown in appendix p 8. By week 12, patients in all the gefapixant dose groups had higher scores on the Leicester Cough Questionnaire, with patients in the 50 mg dose group showing improvement over placebo (table 3, figure 3). In addition to these objective and patient-reported outcomes, patients and physicians were requested

	Placebo (n=61)	Gefapixant		
		7·5 mg (n=59)	20 mg (n=59)	50 mg (n=57)
Cough severity visual analogue scale				
Baseline mean, mm (SD)	57·4 (23·1)	56·7 (20·7)	58·3 (25·1)	57·9 (19·7)
Week 12 mean (SD)	39·3 (28·11)	35·0 (23·60)	34·0 (26·80)	27·9 (22·39)
Week 12 LS mean change from baseline, mm (95% CI)	−16·7 (−22·7 to −10·7)	−21·1 (−27·2 to −15·1)	−23·1 (−29·1 to −17·0)	−27·9 (−34·1 to −21·6)
Week 12 LS mean difference from placebo, mm (95% CI; p value)	..	−4·4 (−12·9 to 4·0; p=0·30)	−6·4 (−14·8 to 2·0; p=0·14)	−11·2 (−19·7 to −2·6; p=0·0108)
Cough severity diary total score				
Baseline mean (SD)	4·1 (1·8)	4·1 (1·7)	4·2 (2·1)	4·3 (1·8)
Week 12 mean (SD)	3·0 (2·12)	2·5 (2·18)	2·4 (2·01)	2·4 (1·76)
Week 12 LS mean change from baseline (95% CI)	−1·2 (−1·6 to −0·7)	−1·5 (−2·0 to −1·1)	−1·7 (−2·2 to −1·3)	−1·9 (−2·4 to −1·4)
Week 12 LS mean difference from placebo (95% CI; p value)	..	−0·4 (−1·0 to 0·3; p=0·25)	−0·6 (−1·2 to 0·0; p=0·07)	−0·7 (−1·4 to −0·1; p=0·0197)
Daily cough score				
Baseline mean (SD)	5·4 (1·8)	5·2 (1·7)	5·5 (1·9)	5·3 (1·7)
Week 12 mean (SD)	3·9 (2·34)	3·3 (2·17)	3·1 (2·30)	3·1 (1·86)
Week 12 LS mean change from baseline (95% CI)	−1·5 (−2·0 to −1·0)	−1·8 (−2·4 to −1·3)	−2·2 (−2·7 to −1·6)	−2·2 (−2·7 to −1·6)
Week 12 LS mean difference from placebo (95% CI; p value)	..	−0·3 (−1·0 to 0·4; p=0·42)	−0·6 (−1·3 to 0·1; p=0·09)	−0·6 (−1·4 to 0·1; p=0·10)
Leicester Cough Questionnaire total score				
Baseline mean (SD)	12·2 (2·8)	12·1 (2·7)	12·0 (3·3)	11·4 (2·8)
Week 12 mean (SD)	13·8 (3·81)	14·8 (3·86)	14·8 (3·90)	15·3 (3·77)
Week 12 LS mean change from baseline (95% CI)	2·1 (1·3 to 3·0)	3·3 (2·4 to 4·2)	3·2 (2·3 to 4·0)	4·0 (3·1 to 4·9)
Week 12 LS mean difference from placebo (95% CI; p value)	..	1·2 (−0·1 to 2·4; p=0·06)	1·0 (−0·2 to 2·3; p=0·10)	1·9 (0·7 to 3·1; p=0·0028)

LS=least squares.

Table 3: **Patient-reported outcomes in the full analysis set after 12 weeks**

to rate their change from baseline at week 12 using the patient Global Impression of Change and clinician's Global Impression of Change endpoints. For the patient's global impression of change, 37 (64·9%) patients on 50 mg gefapixant, 29 (49·2%) patients on 20 mg gefapixant, 31 (53·4%) patients on 7·5 mg gefapixant, and 17 (28·3%) patients on placebo felt that their cough was 'very much improved' or 'much improved'. For the clinician's global impression of change at week 12, clinicians rated that 37 (64·9%) patients taking 50 mg gefapixant, 30 (50·8%) patients taking 20 mg gefapixant, 31 (53·4%) patients taking 7·5 mg gefapixant, and 21 (35%) patients taking placebo had cough that was 'very much improved' or 'much improved'.

The frequency of adverse events, discontinuations due to adverse events, and adverse events determined to be related to treatment all increased in a dose-dependent manner (table 4). Only one patient who was in the 50 mg gefapixant group had a serious adverse event (frostbite). Discontinuations were more frequent at the 50 mg dose due to taste-related adverse events such as ageusia (n=4), hypogeusia (n=2), and dysgeusia (n=2), as well as oral hypoaesthesia (n=2).

Renal and urological adverse events were infrequent and not associated with study treatment. Taste-related adverse events, oral paraesthesia, and oral hypoaesthesia increased in frequency in a dose-dependent manner. Dysgeusia and hypogeusia were the most common adverse events in the study (table 4).

Benefit attributable to gefapixant was not limited to participants experiencing taste adverse events; in a post-hoc analysis, those not reporting taste-related adverse events showed improvements from pre-treatment baseline (with 95% CIs excluding 0), and qualitatively similar to improvements observed among participants who did experience taste adverse events (appendix p 9). However, our study was not powered to discriminate differences in efficacy in patients with and without taste adverse events. Of note, although six (11·8%) patients receiving gefapixant 50 mg felt that their taste effects were extremely bothersome (0% in other dose groups), the acceptability questionnaire responses suggested that patients were no less likely to take any dose of gefapixant than placebo, even for periods of at least 1 year (appendix p 15). This implies that the taste disturbances did not render gefapixant an unacceptable treatment for patients to consider over time periods even longer than those evaluated in this study.

Discussion

Our study shows that gefapixant, a P2X3 receptor antagonist, has antitussive efficacy sustained over a 12-week period. To our knowledge, this is the first study to show that P2X3 antagonism, or indeed any pharmacological intervention, has anti-tussive efficacy sustained over 12 weeks. We found significant improvements not only in objective cough frequency, but also in patient-reported outcomes in the gefapixant 50 mg group compared with placebo. Previous studies of gefapixant confirmed that P2X3 antagonism with a supratherapeutic dose (ie, 600 mg) reduces cough frequency in patients with refractory chronic cough over 2 weeks of treatment,[8] and that gefapixant 100 mg increases the threshold for ATP-evoked cough in patients with chronic cough, suggesting an action on ATP receptors on airway peripheral nerve fibres.[19] A dose-escalation study evaluating doses of gefapixant from 7·5 mg to 200 mg twice daily showed a plateau in dose response that led to the dosing regimen used in the study reported here (7·5 mg to 50 mg).[9] In this study, which included patients with refractory chronic cough or unexplained chronic cough with characteristics typical for a chronic cough population, efficacy was apparent as early as 4 weeks after initiation of treatment. At lower doses of gefapixant (20 mg and 7·5 mg), possible treatment effects were evident at 8 weeks, but changes were not significant at 12 weeks compared with placebo.

	Placebo (n=63)	Gefapixant 7·5 mg (n=63)	Gefapixant 20 mg (n=63)	Gefapixant 50 mg (n=63)	Gefapixant combined (n=189)
Any adverse event	39 (62%)	44 (70%)	54 (86%)	58 (92%)	156 (83%)
Discontinued due to adverse event	2 (3%)	2 (3%)	3 (5%)	10 (16%)	15 (8%)
Serious adverse event	0	0	0	1 (2%)	1 (1%)
Adverse event related to treatment*	22 (35%)	19 (30%)	43 (68%)	55 (87%)	117 (62%)
Adverse events of special interest†					
Renal or urological event	3 (5%)	1 (2%)	2 (3%)	1 (2%)	4 (2%)
Taste related event‡	4 (6%)	6 (10%)	31 (49%)	51 (81%)	88 (47%)
Oral paraesthesia or hypoaesthesia	8 (13%)	6 (10%)	7 (11%)	13 (21%)	26 (14%)
Most common adverse events					
Dysgeusia	3 (5%)	6 (10%)	21 (33%)	30 (48%)	57 (30%)
Hypogeusia	1 (2%)	0	11 (18%)	15 (24%)	26 (14%)
Headache	3 (5%)	4 (6%)	12 (19%)	4 (6%)	20 (11%)
Upper respiratory tract infection	2 (3%)	5 (8%)	9 (14%)	6 (10%)	20 (11%)
Ageusia	1 (2%)	0	3 (5%)	13 (21%)	16 (9%)
Paraesthesia oral	5 (8%)	4 (6%)	5 (8%)	4 (6%)	13 (7%)
Cough	2 (3%)	2 (3%)	5 (8%)	5 (8%)	12 (6%)
Hypoaesthesia oral	3 (5%)	2 (3%)	4 (6%)	5 (8%)	11 (6%)
Nausea	0	0	4 (6%)	6 (10%)	10 (5%)
Urinary tract infection	2 (3%)	3 (5%)	5 (8%)	2 (3%)	10 (5%)

*Adverse events determined by the investigator to be possibly, probably, or definitely related to study treatment. †Prespecified. ‡Taste-related adverse events included dysgeusia, hypogeusia, and ageusia.

Table 4: **Summary of safety and tolerability**

The treatment of patients with refractory chronic cough or unexplained chronic cough is an important unmet clinical need because there are no approved therapies. These conditions have a large negative effect on a patient's quality of life.[20–22] The mean duration of cough in our study was 14·5 years. Several studies have provided some evidence that low-dose morphine sulphate and gabapentin could improve cough-specific quality of life over shorter time periods; however, both therapies are associated with substantial side-effects and neither study evaluated treatment effects objectively using 24-h cough frequency.[4,5] Nonetheless, the improvements in patient-reported outcomes with gefapixant in our study compare favourably with effects previously reported for these unapproved therapies.[4,5]

In our study, gefapixant had a positive safety profile, with only one serious adverse event, deemed to be unrelated to the study drug. Tolerability events, particularly dysgeusia, were the most frequently reported adverse events. Tolerability issues related to taste disturbances showed a clear relationship with the dose of gefapixant. Of note, some patients discontinued therapy as a consequence of taste adverse experiences, but most patients who continued therapy stated that they would continue treatment for at least a year (appendix p 14). Gefapixant is a first-in-class, non-competitive inhibitor of the P2X3 ion channel, with some selectivity for this homomeric channel over heteromeric P2X2/3 channels. In addition to evidence that P2X3 receptors are expressed by airway sensory nerves that activate cough, both P2X3 and P2X2/3 receptors have been described on fibres that innervate taste buds.[23] In rodents, heteromeric P2X2/3 channels are thought to have a central role in mediating taste, which could explain the adverse taste events associated with this therapy.[24] However, the role of P2X3 versus P2X2/3 receptors in mediating taste in humans is not well understood, and it is feasible that in humans, taste alterations associated with gefapixant are largely mediated by inhibition at P2X3 receptors. Our study was not designed to address the question of whether cough reduction can be achieved without taste disturbance with this therapy. Gefapixant is currently being evaluated in phase 3 clinical studies (NCT03449134 and NCT03449147), which will provide further information on this question, as well as overall safety, tolerability, and the acceptability (ie, benefits *vs* side-effects) of gefapixant in a larger sample size treated over a longer period.

This large-scale multicentre cough monitoring study both corroborates and adds to previous data supporting the efficacy of gefapixant in refractory chronic cough and unexplained chronic cough, including an initial proof-of-concept study for the antitussive effects of P2X3 antagonism[8] and investigations of the balance between efficacy and tolerability at lower doses.[9,10] In previous studies, improvements in cough frequency and patient-reported outcomes were shown for much shorter treatment periods of 4–14 days, and for doses as low as gefapixant 15 mg twice daily. The fact that reductions in objective cough frequency observed in this study for the 20 mg and 7·5 mg doses of gefapixant were not significant

might be due to the magnitude of the placebo effect, which was larger than that previously observed. Objective cough monitoring was chosen as the primary endpoint in this study for several reasons. First, cough frequency monitoring provides objective evidence that neuromodulator therapies reduce coughing, rather than just alter the perception of cough severity. Second, cough frequency measures are more sensitive to change than are patient-reported outcomes, which are influenced by subjective effects (eg, mood, vigilance, and personality) that can hamper the ability to see a dose response. These subjective effects might explain why both the cough severity diary score and the Leicester Cough Questionnaire score did not discriminate between the three doses at 12 weeks. Finally, cough monitoring is increasingly required by regulatory agencies in the development of novel antitussive therapies.

This study had several strengths and limitations. Strengths include the use of the ACCP clinical guideline to select patients for our study, the large number recruited, the inclusion of both secondary and tertiary recruitment centres, and recruitment from two different countries; all these factors are likely to make our findings more generalisable to the broader population of patients with refractory or unexplained chronic cough. The characteristics of patients recruited to this study (predominantly females aged approximately 60 years) closely resemble those reported in numerous small interventional studies in refractory and unexplained chronic cough, and in a large observational report describing patients attending cough clinics.[4,5,17,25–27]

In terms of limitations, although the presence of taste disturbances was much lower among patients in the lower-dose groups, it should be acknowledged that this adverse event has the potential to unmask patients to the study medication allocation. However, the use of multiple dose groups provides some protection against unmasking. Additionally, despite the potential for unmasking, participants who received placebo treatment exhibited significant placebo effects, influencing all the endpoints evaluated, including objective cough frequency. Not only were there responders in the placebo group, but there were also patients who reported taste disturbance. In most previous studies testing antitussive agents in refractory or unexplained cough, placebo effects were not reported. Direct comparisons with previous trials are difficult because large-scale, multicentre, parallel-group studies have rarely been done and none has used 24-h objective cough monitoring as an endpoint. Smaller proof-of-concept studies of patients with chronic cough generally used crossover designs and reported little change in patients given placebo.[9,26,27] Knowledge of the previous successful studies of gefapixant, and the greater likelihood (75%) of assignment to a gefapixant group, might have substantially changed expectations for patients participating in this particular trial, contributing to the placebo effect observed.

In conclusion, targeting P2X3 channels with gefapixant at a dose of 50 mg twice daily was safe and generally well tolerated, and significantly reduced cough frequency in patients with refractory chronic cough and unexplained chronic cough after 12 weeks compared with placebo. Gefapixant therefore shows promise as a novel therapy for chronic cough, and further studies examining longer-term antitussive benefit are warranted.

Contributors

The Protocol 012 Investigators participated in the trial and all recruited patients. APF, Y-PL, SSB, MMK, JAS, and LPM contributed to the conception of the study. APF, Y-PL, SSB, JAS, LPM, and MMK contributed to the design of the study. APF, Y-PL, SSB, MMK, JAS, and LPM contributed to the planning of the study. APF, DRM, ZJX, W-CW, Y-PL, SSB, AHM, MMK, JAS, and LPM contributed to interpretation of the results. APF, DRM, SSB, W-CW, MRS, AHM, MMK, JAS, LPM, and Y-PL contributed to critically reviewing or revising the manuscript for important intellectual content. ZJX, W-CW, and Y-PL contributed to the analysis of the data. ZJX, JAS, and LPM contributed to the drafting of the manuscript. SSB, AHM, MMK, JAS, LPM, and MRS contributed to the acquisition of the data. All authors approved the submitted draft, and they vouch for the accuracy and completeness of the data reported and attest that the study was conducted in accordance with the protocol.

Declaration of interests

JAS has received grants and personal fees related to the submitted work from Afferent Pharmaceuticals/Merck & Co., Inc; grants from Ario Pharma, GlaxoSmithKline, NeRRe Pharmaceuticals, Menlo, Bellus, and Bayer; personal fees from Chiesi, Ario Pharma, GlaxoSmithKline, NeRRe Pharmaceuticals, Menlo, Bellus, Bayer, Boehringer Ingleheim, Genentech, and Neomed; non-financial support from Vitalograph; and is a named inventor on a patent, owned by Manchester University NHS Foundation Trust and licensed to Vitalograph Ltd, describing the detection of cough from sound recordings. MMK was an employee of Afferent Pharmaceuticals/ Merck & Co., Inc during the course of this study. AHM has received grants and personal fees from Afferent Pharmaceuticals/Merck & Co. SSB has received grants from Merck & Co., Inc; scientific advisory board and consultancy fees from Merck & Co., Inc, Bayer, Patara, Sanofi, Pfizer, and Menlo; speaker fees from Roche; and grants for travel and subsistence for attendance of scientific meetings from Boehringer Ingelheim. LPM has received grants from Afferent Pharmaceuticals/Merck & Co, NC3Rs, British Heart Foundation, EU Interreg VA Health & Life Science Programme, and Chiesi; personal fees from Afferent Pharmaceuticals/ Merck & Co., Inc, Applied Clinical Intelligence, and AstraZeneca; grants for travel and subsistence for attendance of scientific meetings from Boehringer Ingelheim, GlaxoSmithKline, and Chiesi; and advisory board/consultancy fees from Almirall, NAPP, GlaxoSmithKline, and Boehringer Ingelheim. MRS has received grants and personal fees from Afferent Pharmaceuticals/ Merck & Co., Inc; is a consultant to Bayer, Bellus, and NeRRe Therapeutics; and has done clinical research with Bellus. Y-PL received personal fees from Afferent Pharmaceuticals/Merck & Co. W-CW, ZJX, and DRM are employees of Merck & Co., Inc. APF was the founder of Afferent Pharmaceuticals and is a former employee of Merck & Co., Inc.

Data sharing

The data sharing policy of Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

Acknowledgments

This study was funded by Afferent Pharmaceuticals, which has been acquired by Merck & Co., Inc., Kenilworth, 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). JAS is funded by the NIHR Manchester Biomedical Research Centre and a Wellcome Investigator Award, and is an NIHR senior investigator. Medical writing

support was provided by Anish Mehta (Merck & Co., Inc., Kenilworth, NJ, USA). We also thank Michele McColgan (Merck & Co, Kenilworth, NJ, USA) for additional editorial and administrative support. This assistance was funded by Merck Sharp & Dohme, a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

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