Design and rationale of two phase 3 randomised controlled trials (COUGH-1 and COUGH-2) of gefapixant, a P2X3 receptor antagonist, in refractory or unexplained chronic cough

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ABSTRACT

Background: We present study designs, dose selection and preliminary patient characteristics from two phase 3 clinical trials of gefapixant, a P2X3 receptor antagonist, in refractory chronic cough (RCC) or unexplained chronic cough (UCC).

Methods: COUGH-1 (NCT03449134) and COUGH-2 (NCT03449147) are randomised, placebo-controlled, double-blind, parallel-group trials in subjects with RCC or UCC (age $\geqslant 18$ years; cough duration $\geqslant 1$ year; Cough Severity Visual Analogue Scale score $\geqslant 40$ mm). The primary efficacy study periods are 12 weeks (40-week extension; COUGH-1) and 24 weeks (28-week extension; COUGH-2). Interventions include placebo, gefapixant 15 mg and gefapixant 45 mg (1:1:1 ratio). The primary efficacy endpoints are average 24-h cough frequency at Week 12 (COUGH-1) and Week 24 (COUGH-2). Awake cough frequency, patient-reported outcomes and responder analyses are secondary endpoints.

Results: The doses of 45 mg (to provide maximal efficacy and acceptable tolerability) and 15 mg (to provide acceptable efficacy and improved tolerability) were selected based on phase 1 and 2 studies. In COUGH-1, 730 participants have been randomised and treated; 74% are female with mean age of 59 years (39% over 65 years), and mean baseline duration of cough of 11.5 years. In COUGH-2, 1314 participants have been randomised and treated; 75% are female with mean age of 58 years (33% over 65 years), and mean baseline duration of cough of 11.1 years.

Conclusions: These global studies include participants with baseline characteristics consistent with previous RCC and UCC studies and will inform the efficacy and safety profile of gefapixant in the treatment of patients with RCC and UCC.

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This protocol describes the design of two global, phase 3 studies with >2000 participants with refractory or unexplained chronic cough, designed to confirm efficacy and safety of gefapixant, a P2X3 receptor antagonist, at doses of 45 mg and 15 mg https://bit.ly/2Xzgu74

Introduction

Chronic cough affects up to 10% of the worldwide population [1]. While many chronic cough patients find relief with a proper diagnosis of associated conditions and treatment (*i.e.*, asthma, rhinitis or reflux disease), many others continue coughing even when associated conditions are controlled with medications (*i.e.*, refractory chronic cough (RCC)) or when a diagnosis cannot be found (*i.e.*, unexplained chronic cough (UCC)) [2]. RCC and UCC patients often suffer from physical, social and psychological stress of coughing throughout the day that may last for years. [3, 4] They also undergo multiple, unsuccessful investigations by different physicians and rounds of treatments with minimal to no alleviation from coughing. It has been over half a century since the last approved treatment for cough. Thus, treatment for RCC and UCC is a significant unmet medical need.

The goal of treatment is to reduce, but not completely suppress, cough while avoiding central nervous system (CNS) adverse effects, which may be achieved with more targeted therapies [5]. Many currently available medications target central neurological mechanisms, including opioids [6–8] or dextromethorphan [9], which have adverse effects (*i.e.*, sedation, addiction, gastrointestinal effects, respiratory depression) that may affect tolerability and therefore limit efficacy. While benzonatate is thought to act on peripheral afferent vagal nerve fibres, it may inhibit sodium channels, leading to central effects such as dizziness, unresponsiveness and disorientation [10]. More recently, neuromodulators such as pregabalin and gabapentin have been studied for chronic cough but are also associated with frequent CNS effects [11, 12].

Airway sensory neurons have been a recent area of research into targets that may ameliorate chronic cough including chemically sensitive receptors such as TRPV1 and P2X3 that bind to ligands such as capsaicin and ATP; these receptors respond to both endogenous stimuli produced by mucosal inflammation and exogenous irritants [13–15]. The P2X3 receptor is a purinergic, ligand-gated ion channel that, upon binding with extracellular ATP from airway inflammation, activates vagal C-fibre sensory neurons, thus initiating the cough reflex. This peripheral target may achieve efficacy without CNS effects. Preclinical evidence suggests that afferent vagal C-fibres are chemosensitive rather than mechanosensitive; therefore, P2X3 antagonism is not expected to compromise airway protection from aspiration, but rather treat the pathology of chronic cough. Gefapixant, a P2X3 receptor antagonist, has demonstrated efficacy in reducing objective cough frequency and improving patient-reported outcomes in RCC and UCC patients in studies that evaluated doses from 7.5 mg twice daily to 600 mg twice daily [16–18]. No association with serious adverse events was observed, although taste-related adverse events occurred in dose-dependent fashion.

Here, we describe the design, dose selection methodology and preliminary patient characteristics for two phase 3 studies (COUGH-1 (NCT03449134) and COUGH-2 (NCT03449147)) evaluating the efficacy, tolerability and safety profile of gefapixant at two dose levels, 15 mg and 45 mg twice daily, that may provide clinicians and patients with options that maximise efficacy and minimise taste-related adverse events.

Modelling and simulation for dose selection in phase 3

Phase 3 dosing strategy was based on efficacy, safety and tolerability (*i.e.*, taste-related adverse events) from 12-week data from phase 2 studies (table 1). The pharmacokinetics of gefapixant were best described by a one-compartmental pharmacokinetic model with an elimination half-life of 7–10 h necessitating a twice daily dosing regimen. Renal function, expressed as creatinine clearance, was identified as the major source of variability in plasma exposure. Two different approaches were used to characterise the efficacy, taste-related effects and discontinuation data using quantitative models: one using gefapixant plasma levels as an explanatory variable to model response data (exposure–response (E-R)); another using the dose as the explanatory variable (dose–response).

Multiple candidate dose–response models (linear, log-linear, Emax and sigmoidal Emax models) were evaluated. The objective for dose selection for phase 3 studies was to identify a low dose that would have a projected clinically relevant effect on cough frequency with a low incidence of taste disturbance and a higher dose that would be the lowest dose that could achieve maximal efficacy. The key benefit to this

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TABLE 1 Phase 2 studies in gefapixant for chronic cough				
Study	**Subjects n**	**Design**	**Treatments**	**Summary of results**
Protocol 006 (NCT01432730)	24	Randomised, double-blind, placebo-controlled, crossover study in patients with RCC; subjects were treated for 2 weeks and crossed-over after a 2-week washout	Placebo Gefapixant 600 mg twice daily	Cough frequency was reduced by a placebo-adjusted 75% with gefapixant 600 mg twice daily (p=0.0003). However, all patients who received gefapixant 600 mg twice daily had a taste-related adverse event and 25% of patients discontinued [16].
Protocol 010 (NCT02349425)	59 *Cohort 1: n=29* *Cohort 2: n=30*	Randomised, 2-cohort (high dose and low dose), double-blind, placebo-controlled, crossover, dose-escalation that recruited patients with RCC; subjects were assigned to receive ascending doses of gefapixant or placebo for 16 days (4 days for each dose) then crossed-over after washout	Cohort 1: 50, 100, 150 and 200 mg twice daily or placebo; Cohort 2: 7.5, 15, 30 and 50 mg twice daily or placebo	Reductions in cough frequency with gefapixant appeared to plateau at doses ⩾30 mg; taste-related adverse events appeared to increase in a dose-related manner at doses ⩾30 mg [17]
Protocol 012 (NCT02612610)	253	Randomised, double-blind, placebo-controlled, parallel group, study in RCC or UCC patients; subjects were treated for 12 weeks	Placebo Gefapixant 7.5 mg twice daily Gefapixant 20 mg twice daily Gefapixant 50 mg twice daily	Placebo-adjusted mean percent reduction in awake cough frequency was 22% for 7.5 and 20 mg (not statistically significant) and 37% for 50 mg (p=0.003); 81% of patients in the 50-mg dose group experienced taste-related adverse events, but only ~10% reported taste-related adverse events on 7.5 mg [18].
RCC: refractory chronic cough; UCC: unexplained chronic cough.				

approach is that a strong assumption about the form of the underlying model is not necessary, avoiding having that prescribed model form from heavily impacting the dose-specific estimates. Dose–response estimates for the three endpoints were obtained as a weighted average of the four models fit to these data. The 15-mg dose was predicted to achieve ~20% reduction in 24-h cough frequency (relative to placebo) with ~20% incidence of taste disturbance. A 45-mg dose was predicted to achieve nearly maximal reduction in 24-h cough frequency (relative to placebo), with a predicted discontinuation rate due to adverse events at an acceptable level (~14%) (figure 1). An additional consideration was that 45 mg is a multiple of the low dose of 15 mg providing manufacturing efficiency.

For the E-R approach, simulations using a virtual population (n=250) of interest were performed with final exposure–response models to evaluate the dose–response profiles for cough reduction, taste-related
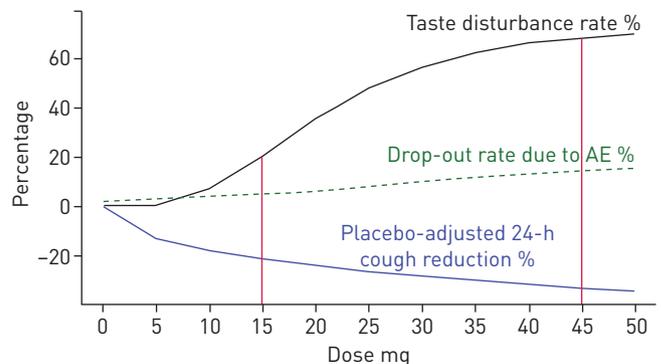
FIGURE 1 Predicted dose–response patterns for efficacy and safety endpoints based on a multiple comparisons procedure after 12 weeks of treatment – modelling (MCP-Mod) approach. AE: adverse event.

adverse events and discontinuations for a dose range of 0–50 mg in steps of 2.5 mg [17, 18]. Simulations were repeated 1000 times by incorporating parameter uncertainty for estimated fixed-effect parameters of the exposure–response models. Simulation results using the E-R model for change in cough frequency, incidence of taste-related adverse events and discontinuations are shown in figure 2. The modelling and simulation data from the phase 2b study (7.5 to 50 mg twice daily) [18] indicate a steep decrease in 24-h cough rate up to ∼15 mg followed by a less steep decrease up to 30 mg and levelling off thereafter. Conversely, the taste disturbance results indicate a steep increase in taste-related adverse events between 10 to 30 mg and plateauing thereafter.

Based on quantitative approaches as well as consideration of varying probabilities of achieving targeted effects with different doses, a low dose of gefapixant 15 mg twice daily is predicted to provide a clinically meaningful reduction in cough frequency with minimal incidence of taste-related adverse events and a minimal rate of discontinuations; a high dose of gefapixant 45 mg twice daily is predicted to provide maximal reduction in cough frequency, with an acceptable rate of taste-related adverse events/ discontinuations.

Phase 3 study designs

COUGH-1 and COUGH-2 are two phase 3, double-blind, randomised, placebo-controlled studies with an anticipated enrollment of over 2000 RCC or UCC participants. The primary hypotheses are that at least one gefapixant dose is superior to placebo in reducing coughs per hour (over 24 h) at Week 12 (COUGH-1) or Week 24 (COUGH-2). In COUGH-1, ∼720 participants were planned to enter the study. In COUGH-2, ∼1290 participants were planned to enter the study. Enrollment has completed with a final randomised and treated number of 730 participants in COUGH-1 and 1314 participants in COUGH-2. The main study periods are 12 weeks for COUGH-1 and 24 weeks for COUGH-2. Extension periods are planned after the main study periods (40 weeks for COUGH-1 and 28 weeks for COUGH-2) during which participants will continue the same treatments they received in the main study periods; no cough count data will be collected during this period, but subjects will continue to complete patient-reported outcomes and to be monitored for safety. A safety follow-up visit will be done 14 days after last dose of study treatment. Discontinued participants will be followed through completion of the study to collect information on adverse events, medication use and assessments of cough (figure 3).

A central interactive response technology system was used for allocation/randomisation to study treatment. Treatment allocation/randomisation was stratified by sex and geographical region. A double-blinding technique with in-house blinding was used. Gefapixant and placebo will be packaged identically, and the participant, the investigator and Sponsor personnel involved in the study medication administration or clinical evaluation of the participants were unaware of the group assignments.

Patient population and inclusion/exclusion criteria
Population of participants with RCC or UCC
Male and female participants ⩾18 years of age with chronic cough ⩾1 year and RCC or UCC diagnosis according to the American College of Chest Physician (ACCP) guidelines [19] were included. RCC participants had a clinical evaluation that suggested an investigator-confirmed/diagnosed comorbid condition that may be associated with chronic cough (*e.g.*, gastroesophageal reflux disease, asthma or upper airway cough syndrome). The participant received appropriate diagnostic work-up and at least 2 months of therapy, prior to screening, according to ACCP guidelines [19], but continues to cough. UCC participants had a clinical evaluation of their cough per ACCP guidelines, and this evaluation suggested no comorbid conditions associated with chronic cough.

Participants were included if they did not have significant lung disease or a chest radiograph/computer tomography scan of the thorax (within 5 years and after chronic cough onset) demonstrating no abnormality significantly contributing to cough. A Cough Severity Visual Analogue Scale (VAS) score of ⩾40 mm at both Screening and Baseline was required. Female participants must not be pregnant or breastfeeding and agreed to contraceptive guidance. Participants should not have donated or lost >1 unit of blood (∼300 mL) within 8 weeks of dosing. Participants should also not have significantly abnormal laboratory tests at screening. Smokers or those who gave up smoking only within 12 months or have a smoking history >20 pack-years were not included.

Preliminary patient characteristics
There were 730 participants randomised and treated in COUGH-1 with a mean age of 59 years, 74% of whom were female, a mean duration of cough of 11.5 years (range from 2 to 59 years), and 59% and 41% were diagnosed with RCC and UCC, respectively. In COUGH-2, there were 1314 participants randomised and treated with a mean age of 58 years, 75% were female, a mean duration of cough of 11.1 years (range
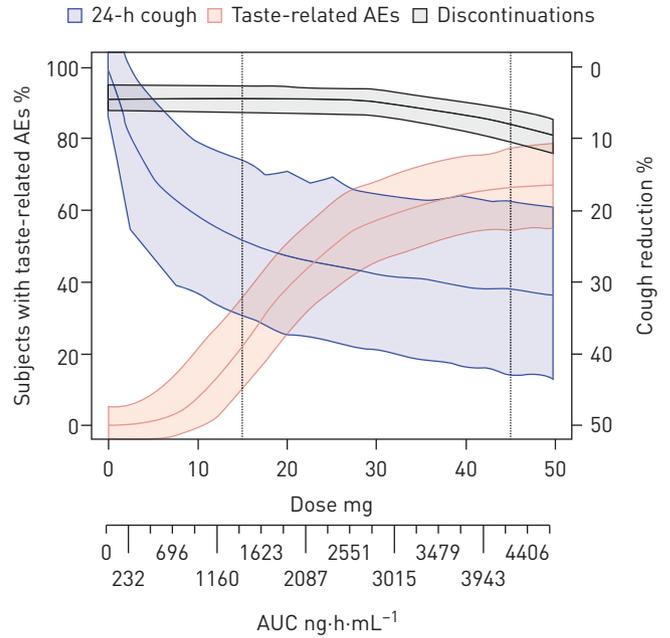
FIGURE 2 Integrated exposure–response profile for cough reduction, taste disturbances and discontinuations. Solid lines represent the median and shaded regions represent the 90% confidence intervals of 1000 trials. The vertical lines represent the responses at 15 and 45 mg. AE: adverse event; AUC: area under the curve.
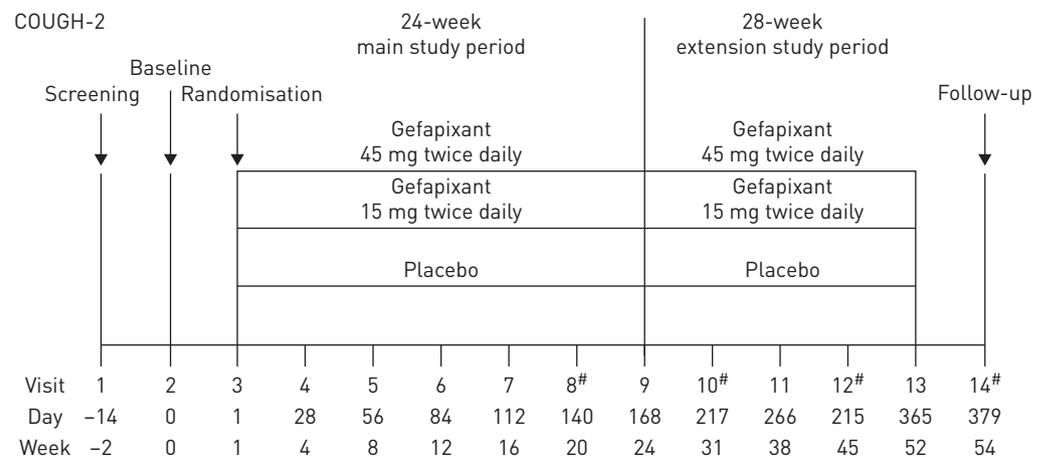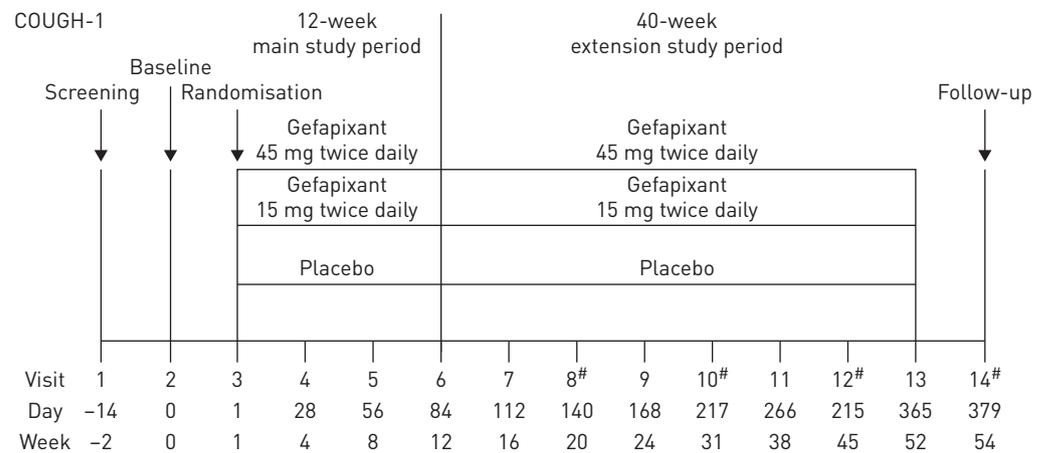
FIGURE 3 Study designs. #: Visits 8, 10, 12 and follow-up visit 14 will be conducted by telephone.

from 1 to 75 years), and 65% and 35% were diagnosed with RCC and UCC, respectively. Over half of randomised participants were in Europe, approximately a quarter in North America, and the other quarter were in Asia Pacific or Other regions (table 2).

Efficacy outcome measures

Objective cough monitoring

Cough counts were measured using a digital recording device (VitaloJAK™; Vitalograph Ltd, Buckingham, UK), which includes microphones affixed to the participant's chest and attached to the participant's clothing. It provides acoustic recordings and facilitates signal processing to accurately identify and quantify cough [20]. Digital recordings will be processed at the Vitalograph centralised reading centre, where recordings are condensed using a computer algorithm before human analysts identify and tag individual coughs. The output of this process is a count of coughs for each 24-h recording period. Objective cough frequency will be evaluated for the 24-h period (24-h Cough Frequency) as well as during waking hours (Awake Cough Frequency).

TABLE 2 Preliminary baseline characteristics		
	COUGH-1	**COUGH-2**
Subjects in population n	730	1314
Sex n (%)		
Male	188 (25.8)	339 (25.1)
Female	542 (74.2)	984 (74.9)
Age years		
<65 n (%)	446 (61.1)	881 (67.0)
⩾65 n (%)	284 (38.9)	433 (33.0)
Mean	59.0	58.1
SD	12.6	12.1
Median	61.0	60.0
Range	19–89	19–88
Race n (%)		
American Indian or Alaska Native	21 (2.9)	73 (5.6)
Asian	104 (14.2)	44 (3.3)
Black or African American	11 (1.5)	28 (2.1)
Multiple	24 (3.3)	103 (7.8)
White	570 (78.1)	1057 (80.4)
Body mass index kg·m^{-2}		
Subjects with data	730	1309
Mean	28.24	28.78
SD	5.75	5.84
Median	27.60	27.86
Range	16–54	13–56
Duration of chronic cough years		
Subjects with data	730	1288
Mean	11.54	11.06
SD	9.45	9.84
Median	9.00	8.00
Range	2–59	1–75
Region n (%)		
Asia Pacific	103 (14.1)	81 (6.2)
Europe	365 (50.0)	714 (54.3)
North America	167 (22.9)	298 (22.4)
Others	95 (13.0)	224 (17.0)
Primary diagnosis n (%)		
Refractory chronic cough	430 (58.9)	851 (64.8)
Unexplained chronic cough	300 (41.1)	459 (34.9)
Missing	0	4 (0.3)
Most common comorbid conditions n (%)		
Asthma	312 (42.7)	532 (40.5)
Allergic rhinitis	145 (19.9)	191 (14.5)
Gastroesophageal reflux disease	294 (40.3)	530 (40.3)

Patient-reported outcomes

At screening, each participant was trained and instructed on the use of an electronic diary (eDiary) for completing electronic patient-reported outcome (ePRO) measures. Table 3 includes details on patient-reported outcomes (PROs) evaluated in the studies.

Daily cough severity VAS and cough severity diary (CSD) assessments were recorded as daily electronic ePRO measures using eDiary. Subjects were to bring their eDiaries to all study visits.

Responder analyses

Responder analyses were planned, with responders defined as participants who achieved ⩾30% reduction in 24-h cough frequency [22]. Definitions for responders for PROs are given in table 3.

Primary and secondary endpoints

The primary efficacy endpoints are the mean change from baseline in 24-h cough frequency (coughs/hour) at Week 12 (COUGH-1) and at Week 24 (COUGH-2). The assessment of 24-h coughs per hour are calculated as the total number of cough events during the monitoring period (24-h interval)/24 h. Cough frequency is determined using the VitaloJAK cough monitor.

The assessments of Awake Cough Frequency at Week 12 (COUGH-1) and Week 24 (COUGH-2) are secondary endpoints. Awake coughs per hour=total number of cough events during the monitoring period (24-h interval) the participant is awake/total duration (in hours) for the monitoring period the participant is awake.

Additional secondary endpoints include the responder analyses (responders defined above) for 24-h cough frequency, CSD, cough severity VAS, and Leicester Cough Questionnaire (LCQ).

Safety and tolerability

Safety and tolerability were assessed by clinical evaluation of adverse events and inspection of vital signs, physical examination and standard laboratory safety tests. Relationship of adverse events to study medication, seriousness and discontinuations due to adverse events were quantified. Taste-related adverse events (dysgeusia, ageusia, hypogeusia or related terms) were evaluated and analysed.

Analyses of adverse events

Adverse events of special interest including taste-related adverse events will be subject to inferential testing for statistical significance with unadjusted p-values and 95% confidence intervals provided for between-group comparisons. The broad adverse event categories of participants with any adverse event, drug-related adverse events, serious adverse events, drug-related and serious adverse events, oral paraesthesias, oral hypoaesthesia adverse events and discontinuations due to adverse events will be evaluated *via* point estimates and 95% confidence intervals for between-group comparisons. Other adverse events that will be evaluated with point estimates and 95% confidence intervals for between-group comparisons include adverse events with at least four participants in any treatment group exhibiting the adverse event. The confidence intervals should be regarded as a descriptive measure rather than a formal method for assessing the statistical significance since there is no adjustment for multiplicity. All other adverse events and predefined limits of change will be evaluated *via* point estimates only.

Statistical analyses

The sample sizes were to be 720 (COUGH-1) and 1290 (COUGH-2) participants. COUGH-1 was powered at ⩾89% for pairwise comparisons of both doses to placebo for 12-week 24-h and awake cough frequency, and % participants with ⩾30% reduction in 24-h cough frequency (the latter endpoint being powered only for 45 mg *versus* placebo). COUGH-2 was powered at ⩾80% for pairwise comparisons of both doses to placebo for (all at 24 weeks) 24-h cough frequency, awake cough frequency, and % participants with ⩾1.3-point increase in the LCQ relative to baseline (the latter endpoint being powered only for 45 mg *versus* placebo).

For efficacy analyses, the primary population is the Full Analysis Set (all randomised participants who have taken at least one dose of study medication and provided at least one baseline and at least one post-baseline endpoint observation during the treatment period). For safety analyses, the population is All Patients as Treated (all randomised participants who received at least one dose of study medication, at least one laboratory or vital sign measurement obtained subsequent to at least one dose of study intervention). A baseline measurement is required to assess change from baseline.

The primary analysis of the primary endpoint will be on the natural log scale of the cough rate data. The variable of change from baseline in log-transformed 24-h coughs per hour will be used in the analysis of

PRO name	Description	Responder definition
Leicester Cough Questionnaire (LCQ)	The LCQ includes 3 domains: physical, psychological and social. Domain scores (range 1–7) are the sum of individual item scores divided by the number of items in the domain; total LCQ score (range 3–21) is the sum of the 3 domain scores	Change from baseline in LCQ total score of ⩾1.3 points [21]
Cough Severity VAS	Subjects scored cough severity from 0 to 100 using a VAS	⩾30 mm reduction in Cough Severity VAS score (data on file/manuscript in preparation)
Cough Severity Diary (CSD)	The CSD includes 7 items, each with scores ranging from 0 (best) to 10 (worst). The total daily CSD score is the sum of these 7 item scores. Mean total daily scores are the sum of 7 item scores divided by 7; 3 subscales (cough frequency, intensity and disruption) were derived for each day	Change from baseline in mean weekly CSD total score of ⩾1.3-point reduction as the first threshold and ⩾2.7-point reduction as the second threshold [12]
Patient Global Impression of Change Questionnaire (PGIC)	The rate of change in participants' chronic cough compared to the start of the study will be assessed using the PGIC with response options ranging from "very much improved" to "very much worse"	N/A
Hull Airway Reflux Questionnaire (HARQ)	The HARQ is used to more completely characterise the patient population and consists of 14 questions with responses on a numeric scale from 0 to 5. A score of "0" means that no problems are caused by the cough symptom and "5" means severe/frequent problems	N/A
12-item Short Form Survey (SF-12)	The SF-12 is a validated, 12-item questionnaire designed to assess general health-related quality of life. It is a widely used instrument that has been shown to be responsive to changes in disease severity following intervention. The SF-12 is scored such that a total score and 8 domain scores can be calculated with higher scores indicating better functioning: Physical Functioning, Role Physical, Role-Emotional, Bodily Pain, General Health, Social Functioning, Mental Health and Vitality. Data obtained from the SF-12 will be used in health economic analyses	N/A
EuroQoL 5 L Dimensions Questionnaire	The EQ5D-5 L is a standardised instrument for measuring generic health status used for estimating preference weights for that health status. By combining the weight with time, quality adjusted life years can be computed. The EQ5D-5 L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels and the participant will be asked to indicate their health state using a 5-level rating scale. The EQ VAS records the participant's self-rated health on a vertical VAS where the endpoints are labelled "best imaginable health state" and "worst imaginable health state". This information can be used as a quantitative measure of health outcome as judged by the individual patient	N/A
Work Productivity and Activity Impairment Questionnaire (WPAI)	The impact of cough on work productivity and activity will be assessed with the WPAI questionnaire, which provides an assessment on the following: 1) absenteeism (work time missed); 2) presenteeism (impairment at work/reduced on-the-job effectiveness); 3) work productivity loss (overall work impairment/absenteeism plus presenteeism); and 4) activity impairment. The WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, *i.e.*, worse outcomes. Participants will be	N/A

TABLE 3 Continued		
PRO name	**Description**	**Responder definition**
	asked to indicate if they are currently employed and to respond to the following questions referring to "the past 7 days": work hours missed due to health problems, work hours missed for other reasons, hours actually worked, the degree to which their health has affected productivity while working, and the degree to which their health affected productivity in regular unpaid activities	

PRO: patient-reported outcome; VAS: Visual Analogue Scale.

the primary endpoint. The primary analysis approach will be conducted utilising the longitudinal ANCOVA model. In this model, the response vector consists of the change from baseline in log-transformed 24-h coughs per hour at each post-baseline visit. The model will include factors for treatment group, visit, the interaction of treatment group by visit, sex and region; and the log-transformed baseline value and the interaction of log-transformed baseline value by visit as covariates.

The least squares mean change from baseline (in log scale) with associated standard errors will be displayed for each treatment group. Estimated treatment differences (gefapixant − placebo) along with corresponding 95% confidence intervals will also be presented for each gefapixant treatment group. In addition, the geometric mean of the 24-h coughs per hour will be presented by treatment group and by visit. The percent difference in the change from baseline between gefapixant and placebo will be estimated by $100*(e^{diff} − 1)$, where diff is the difference provided by the analysis of the log-transformed variable.

The continuous secondary efficacy endpoints will be analysed using a similar longitudinal ANCOVA model as used for the primary efficacy analysis.

Discussion

A cross-sectional survey of over 1000 chronic cough patients showed that almost all reported diminished quality of life and only 7% reported that cough medications were effective, thus characterising the nature of the unmet clinical need [3]. COUGH-1 and COUGH-2 are the first phase 3 studies in chronic cough, which represents a major development for RCC and UCC patients; the confirmation of the clinical profile of gefapixant from randomised controlled trials with over 2000 participants would likely lead to a licensed treatment fulfilling an unmet medical need.

These near-replicate studies randomised and treated 2044 global participants with RCC or UCC from North, Central and South America, Europe and Asia. The size and global nature of these studies are unprecedented in this patient population as is the duration of treatment and follow-up. The base period of COUGH-1 will evaluate participants for 3 months while the base period of COUGH-2 will evaluate participants for 6 months; both studies will have extension periods for a total of 52 weeks of treatment. The preliminary patient characteristics are consistent with the profile that has emerged for patients with chronic cough in clinical and observational studies. The characteristics are consistent between COUGH-1 and COUGH-2 as well as an earlier phase 2b study with gefapixant in RCC and UCC patients [18]. Notably, the characteristics are consistent with a worldwide survey of 10 032 patients with chronic cough and characterised as having cough hypersensitivity syndrome (CHS); specifically, most patients tend to be female and over 50 with the most common age group being those over 60. The common characteristics were consistent throughout the world suggesting a distinct clinical entity [2].

Both objective and subjective measures are important when evaluating novel cough medications to measure different aspects of patient burden. Objective cough counting evaluates a pharmacological effect in reducing cough frequency. Only recently have technological improvements made objective cough counting feasible or practical for large trials; in these trials, the VitaloJAK recording device is used to monitor objective cough counts [20]. Subjective patient-reported endpoints help articulate the meaning of cough frequency reduction with regard to the effect that treatments have on the lives of patients. The subjective tools, including cough severity VAS, LCQ and CSD, are well-established measures of cough [23–25]. Measures such as Work Productivity and Activity Impairment Questionnaire (WPAI) will contribute important data on the possible health economic effects of chronic cough and for a potentially effective medication for this condition. The Hull Airway Reflux Questionnaire (HARQ) is included to help

characterise the patients included in these studies and potential triggers for their cough [26]. Cough hypersensitivity syndrome is a term describing chronic cough patients regarding common characteristics, in particular normally non-tussive triggers that are captured with HARQ [26]. However, CHS is a general concept of similar characteristics rather than a diagnosis; patients were enrolled in COUGH-1 and COUGH-2 based on RCC and UCC diagnoses according to ACCP guidelines [19].

A goal for phase 3 was to evaluate two doses that would allow flexibility in treatment. We implemented exposure–response modelling as a traditional approach as well as a complementary approach with MCP-Mod, which is recommended by both the European Medicines Agency Committee for Medicinal Products for Human Use and the US Food and Drug Administration for the assessment of optimal doses in clinical development. The 45 mg twice daily dose is predicted to provide maximal efficacy with acceptable tolerability, while 15 mg twice daily is predicted to provide acceptable efficacy with minimal taste effects.

This global phase 3 development programme aims to provide pivotal data that will inform efficacy and safety of gefapixant in the treatment of patients with RCC and UCC, a population that experiences diminished quality of life, negative work and social effects, and health economic difficulties due to repeated investigations and trials of various medications that do not provide relief.

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