Eliapixant (BAY 1817080), a P2X3 receptor antagonist, in refractory chronic cough: a randomised, placebo-controlled, crossover phase 2a study

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The highly selective P2X3 antagonist eliapixant (BAY 1817080) significantly reduced cough frequency and severity in patients with refractory chronic cough. Mild taste-related adverse events were reported in 5–21% of patients, depending on the dose. https://bit.ly/3afVlVM

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Abstract

Background ATP acting *via* P2X3 receptors is an important mediator of refractory chronic cough (RCC). This phase 2a double-blinded crossover study assessed the safety, tolerability and efficacy of eliapixant (BAY 1817080), a selective P2X3 receptor antagonist, in adults with RCC attending specialist centres.

Methods In period A, patients received placebo for 2 weeks then eliapixant 10 mg for 1 week. In period B, patients received eliapixant 50, 200 and 750 mg twice daily for 1 week per dose level. Patients were randomised 1:1 to period A–B (n=20) or B–A (n=20). The primary efficacy end-point was change in cough frequency assessed over 24 h. The primary safety end-point was frequency and severity of adverse events (AEs).

Results 37 patients completed randomised therapy. Mean cough frequency fell by 17.4% *versus* baseline with placebo. Eliapixant reduced cough frequency at doses ⩾50 mg (reduction *versus* placebo at 750 mg: 25% (90% CI 11.5–36.5%); p=0.002). Doses ⩾50 mg also significantly reduced cough severity. AEs, mostly mild or moderate, were reported in 65% of patients with placebo and 41–49% receiving eliapixant. Cumulative rates of taste-related AEs were 3% with placebo and 5–21% with eliapixant; all were mild.

Conclusions Selective P2X3 antagonism with eliapixant significantly reduced cough frequency and severity, confirming this as a viable therapeutic pathway for RCC. Taste-related side-effects were lower at therapeutic doses than with the less selective P2X3 antagonist gefapixant. Selective P2X3 antagonism appears to be a novel therapeutic approach for RCC.

Introduction

Chronic cough is generally defined as a cough lasting for ⩾8 weeks [1, 2] and is estimated to affect ∼10% of all adults [3, 4]. Cough that persists despite standard therapy for potential underlying treatable traits is known as refractory chronic cough (RCC). In some cases, no clear underlying pathology is elicited (unexplained chronic cough (UCC)). The same empirical treatment regimen is often applied for UCC or RCC and therefore, for simplicity, both groups are referred to here as RCC. RCC has substantial effects on physical and psychological quality of life [5, 6], including stress urinary incontinence, interference with speech and depression. There is a lack of licensed treatments for RCC, and off-label treatments such as opiates, tricyclic antidepressants, pregabalin and gabapentin have limited efficacy and can be associated with adverse effects [7].

Dysregulation of neuronal pathways of the cough reflex is an underlying pathophysiology in RCC [8, 9]. Recent evidence suggests that ATP activating purinergic P2X3 receptors is an important mediator in RCC [10–14]. P2X receptors consist of three transmembrane protein subunits forming an ion channel [15–18]. Seven subunits, numbered P2X1 to P2X7, have been identified. P2X3 receptors occur as homotrimers (*e.g.* with three P2X3 subunits, termed a P2X3 receptor) or heterotrimers (*e.g.* with two P2X3 subunits and one P2X2 subunit, termed a P2X2/3 receptor) [15–18]. P2X3 receptors are predominantly expressed on small-to-medium diameter afferent vagal C or Aδ fibres. Activation of these fibres by P2X3 receptor-dependent ATP signalling has been demonstrated in cell culture and *in vivo* models [8, 19].

A change in the cough reflex from physiological (defensive) to excessive pathological (hypersensitivity) involves both peripheral and central neuronal adaption. This enhanced responsiveness reflects functional changes in nerves and signalling receptors, including P2X3, and consequent upregulation of sensory neuronal activity [9, 20–23]. The role of P2X3 receptors in the pathophysiology of chronic cough is well supported by trials of the P2X3 and P2X2/3 receptor antagonist gefapixant (AF-219; MK7264) [10, 13, 20, 23, 24]. Use of gefapixant has been limited to some extent by significant dysgeusia, attributed to action on the P2X2/3 receptor [13, 14, 23, 24]. If the benefits on cough are mainly mediated by the P2X3 component, which is currently unknown, highly selective P2X3 receptor antagonists may represent a promising novel class of antitussives with potential for fewer side-effects [8, 18]. *In vitro* studies of eliapixant (BAY 1817080), a novel P2X3 receptor antagonist, showed that it has high selectivity for P2X3 receptors over P2X2/3 receptors (Bayer, data on file). Eliapixant is well tolerated in healthy volunteers after single and multiple dosing, and is under investigation in multiple indications involving nerve hypersensitisation (Bayer, data on file). Here we report a phase 2a study of eliapixant in RCC.

Methods

Study overview and design

This was a two-part, double-blinded, placebo-controlled, randomised, parallel-group study (ClinicalTrials.gov: NCT03310645). Part 1, a phase 1 multiple dose escalation study in healthy volunteers investigating the safety, tolerability, pharmacodynamics and pharmacokinetics of doses of eliapixant between 10 and 750 mg over 14 days, will be reported elsewhere. Part 2, reported here, was a two-way crossover phase 2a study of four different doses of eliapixant in patients with RCC, conducted between 29 June 2018 (first informed consent) and 28 May 2019 (last visit), following finalisation of part 1.

The protocol for this study is not publicly available, but redacted information is available on request.

Participants

Patients were recruited from six UK centres by investigators experienced in the management of chronic cough. Eligible patients were aged >18 years, with body mass index (BMI) 18–35 $kg \cdot m^{-2}$, diagnosed with RCC for ⩾1 year, unresponsive to treatment according to the 2006 British Thoracic Society guidelines [25] and a score >40 mm on the cough severity visual analogue scale (VAS) at screening. To accelerate recruitment, patients previously treated with P2X3 receptor antagonists were eligible as long as any prior investigational drug was received at least 2 months (or ∼5 half-lives of the drug if >2 months) before the first dose of study drug in the present study. Patients with forced expiratory volume in 1 s or forced vital capacity <60% of predicted normal at screening were excluded. Patients were also excluded if they had received any systemic or topically active drug that modulates cough within 14 days before first study drug administration or during the trial until the follow-up examination. Full inclusion and exclusion criteria are shown in supplementary table S1.

Procedures

Two treatment periods were employed. In period A, patients received placebo for 2 weeks followed by eliapixant 10 mg for 1 week. In period B, patients received eliapixant in escalating doses of 50, 200 and 750 mg for 1 week per dose level. Patients were randomised 1:1 to period A crossing over to B or *vice versa*, with a 3–4-week washout period between sequences (figure 1). Inclusion of the 10 mg eliapixant dosage in period A allowed four dosages to be evaluated while reducing the study duration and the burden on participants. As a treatment time of 1 week for each dosage of eliapixant had been chosen, a 2-week placebo period was necessary to give an equal duration (3 weeks) for periods A and B.

Eliapixant, as 10, 25 or 150 mg coated tablets, was administered twice daily under fed conditions, except for day 1 of each period when the dose was given three times to shorten time to steady state. Study visits

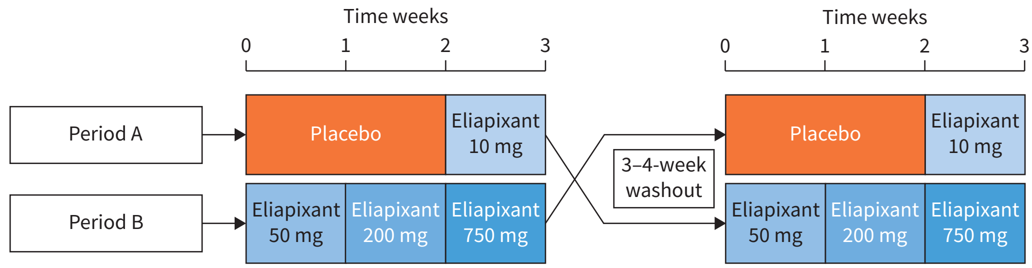

FIGURE 1 Study design.

took place at baseline and on the last day of each treatment week (days 6, 13 and 20); patients were therefore assessed at the end of week 1 and week 2 of placebo treatment. Cough monitoring and assessment of blood pressure and ECG took place at each visit. Adverse events (AEs) were monitored throughout the study. Taste-related AEs were assessed at first occurrence (as standard for crossover studies), and in a cumulative assessment in which events that started at one dose level and persisted into the next were counted again at each dose for which they were present. Taste-related AEs included hypogeusia (quantitative reduction in taste sensation), ageusia (complete loss of sense of taste), parageusia (changed qualitative perception of taste qualities) and dysgeusia (any alteration in taste not otherwise specified) [26].

Outcomes

The primary efficacy end-point was the change in cough frequency per hour, assessed objectively over 24-h periods using a cough recorder (VitaloJAK; Vitalograph, Maids Moreton, UK) [27, 28]. In each study period, cough frequency was assessed pre-dose (day 1) and at the end of each treatment week (days 7, 14 and 21). Hourly cough frequencies while awake and asleep were also assessed. Other key efficacy end-points were patient-reported cough severity and cough-related quality of life, assessed by 100-mm VAS and Leicester Cough Questionnaire (LCQ), respectively. The primary safety end-point was the frequency and severity of AEs. Pharmacokinetic analyses were performed by validated chromatographic methods using a sparse sampling protocol on blood samples taken at 2, 4 and 6 h post-dose on day 0, and at 0, 2, 4, 6 and 23.5 h post-dose on days 6, 13 and 20.

Study oversight and approvals

The protocol and all amendments were reviewed and approved by the West London and GTAC (Gene Therapy Advisory Committee) Research Ethics Committee of the Health Research Authority (17/LO/1103) before the start of the study. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonisation guideline on Good Clinical Practice. All patients were informed about the observed safety and tolerability profile from phase 1, were warned about the possibility of taste-related AEs based on published experience with gefapixant and provided written informed consent.

Randomisation, blinding and statistical techniques

Since the study was a proof-of-concept study, a Bayesian approach with noninformative prior distributions was used for statistical analysis. Results were reported presenting 90% credible limits, which are equivalent to frequentist analyses with 90% confidence intervals. For the (Bayesian) ANCOVA on the primary end-points, two different baselines were used for each patient: the first baseline before period A and the second baseline before period B. This approach was chosen due to the crossover design, because it allows adjustment for unequal carryover effects. Changes from baseline and changes *versus* placebo were determined from paired data using suitable contrasts. Percentages were rounded to the nearest integer and totals may therefore not sum to 100%. Randomisation, blinding and statistical techniques are described further in the supplementary material.

Results

Patient characteristics and disposition

In total, 61 patients were enrolled. After exclusion of 21 screening failures, 40 were randomised: 20 to treatment sequence A–B and 20 to treatment sequence B–A (figure 2). The study was completed according to protocol. Two patients (5%) discontinued study drug because of AEs (see Safety section) and one patient withdrew for personal reasons. In total, therefore, 37 patients completed randomised treatment. All

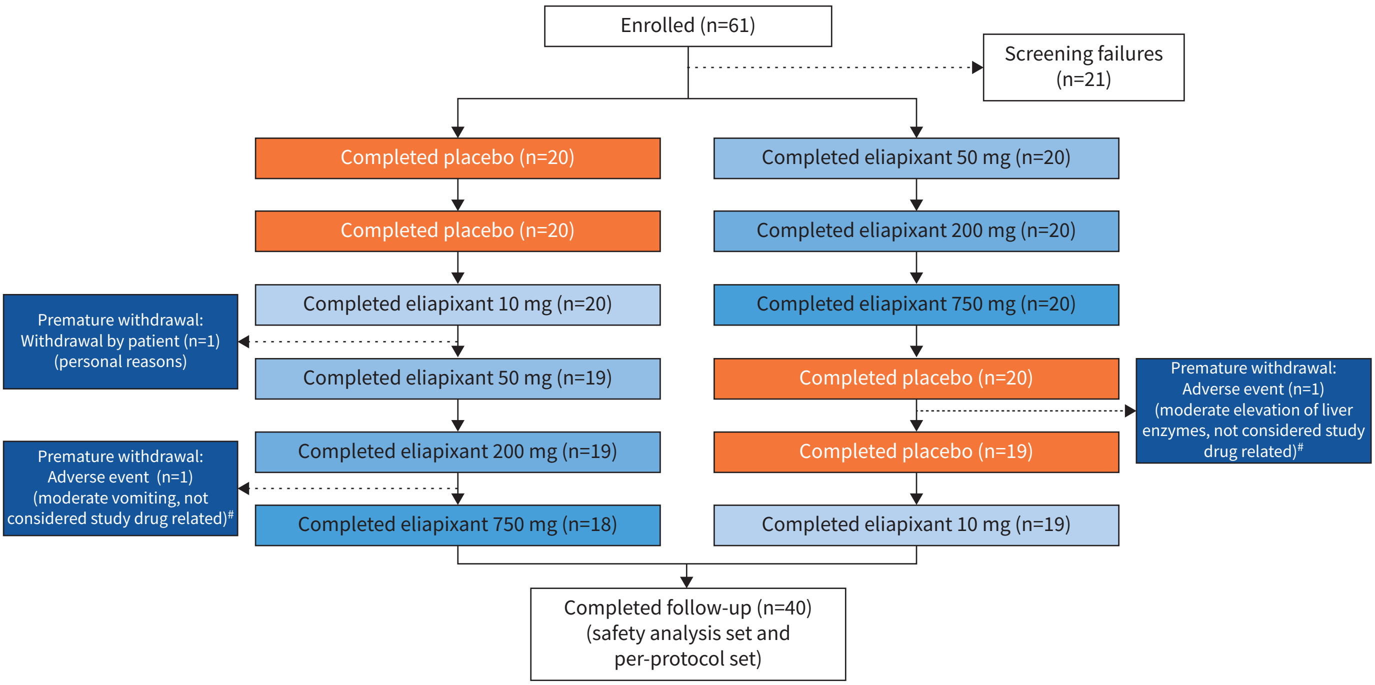

FIGURE 2 Patient disposition. #: investigator assessment.

40 patients completed follow-up and were included in the safety set, and were also eligible for efficacy and pharmacokinetic evaluations (per-protocol set). During the study, 37 patients (93%) received concomitant medication, most commonly paracetamol (as a single drug in 17 patients (43%)). Indications for paracetamol included AEs such as headache (nine patients (23%)) and concomitant disease such as arthritis. Baseline characteristics were similar between the sequence groups (table 1).

TABLE 1 Baseline characteristics of patients (safety population)

	Sequence A–B	Sequence B–A	Total
Patients	20	20	40
Sex			
Male	6 (30)	3 (15)	9 (23)
Female	14 (70)	17 (85)	31 (78)
Race			
Black or African American	1 (5)	0	1 (3)
White	19 (95)	20 (100)	39 (98)
Age years	60.6±13.2	62.4±7.0	61.5±10.5
Range	20–76	50–75	20–76
BMI kg·m^{-2}	26.7±3.1	26.9±3.7	26.8±3.4
Smoking history			
Never-smoker	14 (70)	11 (55)	25 (63)
Ex-smoker	6 (30)	9 (45)	15 (38)
Prior medication#	17 (85)	15 (75)	32 (80)
Geometric mean cough frequency h^{-1} (90% CL)			
24-h	25.4 (17.9–36.0)	24.6 (17.3–34.9)	24.9 (19.5–32.0)
Awake	33.7 (23.6–48.1)	32.1 (22.5–45.9)	32.9 (25.6–42.3)
Asleep	1.8 (1.1–2.8)	2.0 (1.3–3.3)	1.9 (1.3–2.7)
Cough severity VAS mm (90% CL)	72.2 (64.9–79.6)	70.6 (63.3–78.0)	71.4 (66.2–76.7)
LCQ total score (90% CL)	11.2 (9.9–12.5)	10.7 (9.5–12.0)	11.0 (10.0–11.9)

Data are presented as n, n (%) or mean±SD, unless otherwise stated. BMI: body mass index; CL: credible limit; VAS: visual analogue scale; LCQ: Leicester Cough Questionnaire. #: any prior medication used within 4 weeks before the screening visit.

Efficacy

Cough frequency (measured over 24 h) decreased by a mean of 17.4% *versus* baseline with placebo and by 9.4–38.1% *versus* baseline with eliapixant (supplementary tables S2 and S3, and figure 3a). Placebo-corrected changes with eliapixant ranged from +9.5% to −25.0% (supplementary tables S2 and S3, and figure 3b). Awake cough frequency decreased by a mean of 13.9% *versus* baseline with placebo and by up to 36.4% *versus* baseline with eliapixant in a dose-related manner (supplementary tables S2 and S3, and figure 3c). Placebo-corrected changes in awake cough frequency with eliapixant ranged from +5.2% to −26.1% (supplementary tables S2 and S3, and figure 3d). No relevant period effects were observed, but pronounced sequence-by-period interactions were observed. However, both types of effects were accounted for in the statistical model by using different baselines for each period. Geometric mean cough frequencies are shown in supplementary figure S1.

In a *post hoc* analysis the placebo adjustment as performed for trials of other P2X3 receptor antagonists [29], in which arithmetic rather than geometric means appear to have been used, was applied. In this analysis, cough frequency over 24 h and awake cough frequency were reduced by 30.6% and 32.1% *versus* placebo, respectively, with the 750 mg dose (supplementary figure S2).

Cough severity showed a dose-dependent reduction with eliapixant (supplementary tables S4 and S5, and figure 4). Absolute cough severities are shown in supplementary figure S3.

Doses of eliapixant ⩾50 mg increased the LCQ score (representing improvement) *versus* baseline and *versus* placebo (supplementary tables S6 and S7, and figure 5).

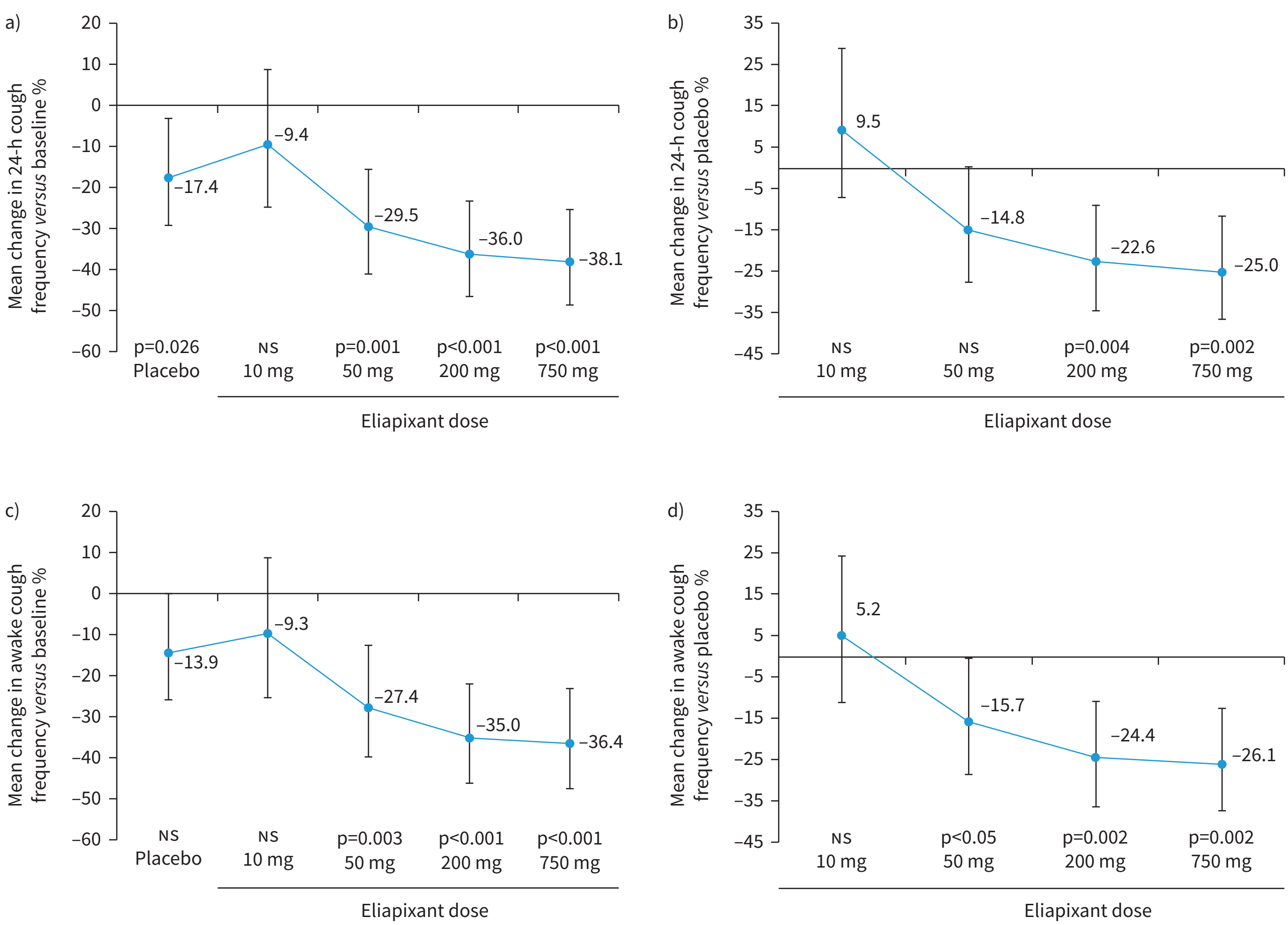

FIGURE 3 Mean changes in a, b) 24-h cough frequency and c, d) awake cough frequency *versus* a, c) baseline and b, d) placebo. Bayesian mixed model analysis (n=40); vertical bars represent 90% credible limits. Treatment time with each dose of eliapixant was 1 week. NS: nonsignificant.

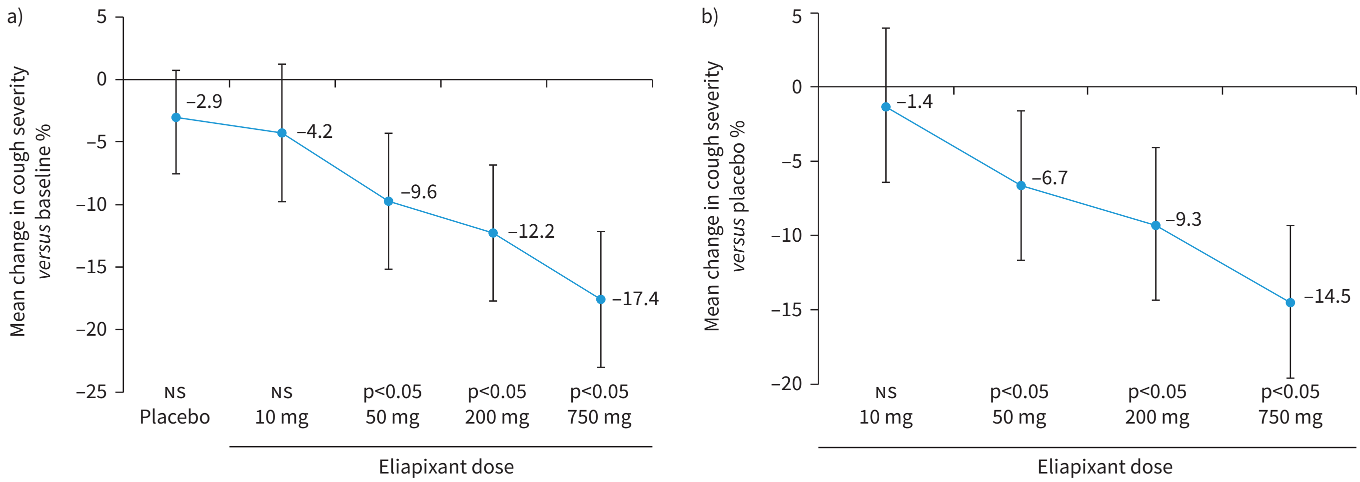

FIGURE 4 Mean changes in patient-reported cough severity (visual analogue scale) *versus* a) baseline and b) placebo. Point estimates; vertical lines represent 90% credible limits. One-sided p-values are shown. Treatment time with each dose of eliapixant was 1 week. NS: nonsignificant.

During the treatment phases, no patient took gabapentin, amitriptyline, opioids or any other drugs shown to affect RCC.

Safety

AEs were reported in 65% of patients with placebo and 41–49% of patients receiving eliapixant, with no dose relationship (table 2). Most AEs were mild or moderate in severity. AEs considered study drug related by the investigator were reported in 13% of patients with placebo and 0–21% of patients receiving eliapixant, with no dose relationship (table 2). The most common study drug-related AEs overall were dysgeusia (n=9 (23%)) and headache (n=4 (10%)) (supplementary table S8). Two patients discontinued study drug because of AEs: one with vomiting of moderate intensity while receiving eliapixant 200 mg and one with moderate increases in liver enzymes while receiving placebo. The latter patient was subsequently diagnosed with pancreatitis due to a stone in the common bile duct. This was the only serious and severe AE reported during the study. Neither event leading to discontinuation was considered related to study drug by the investigator. No deaths occurred during the study. No clinically relevant changes in laboratory parameters or vital signs other than those mentioned were reported (data not shown).

The most frequently reported AEs overall were headache, dysgeusia, fatigue and diarrhoea (table 3). Dysgeusia, in terms of the first occurrence of the event, was reported in 8–10% of patients receiving

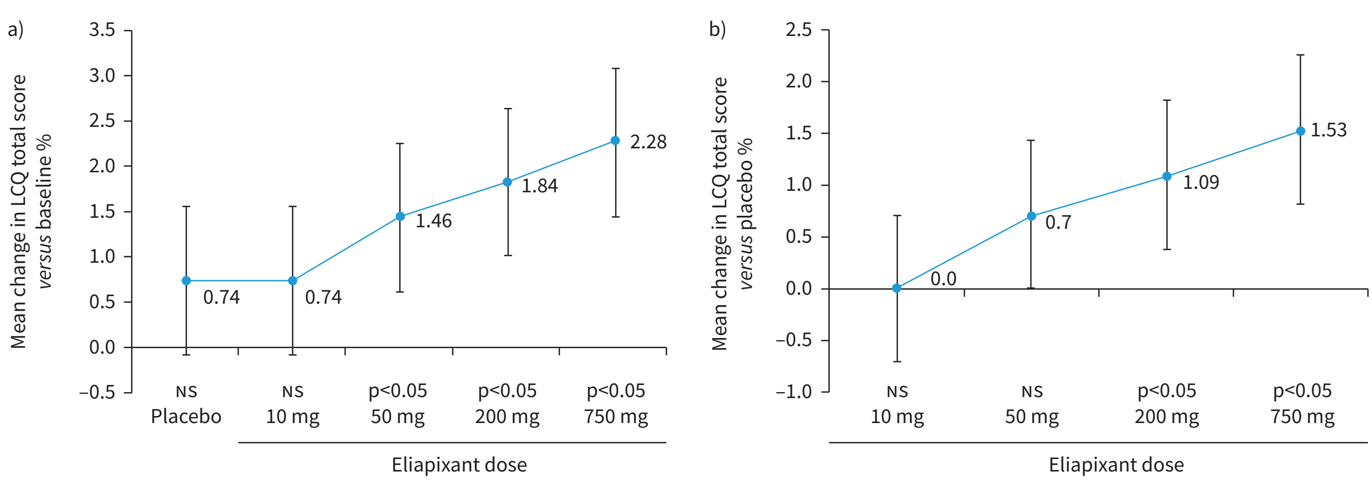

FIGURE 5 Mean changes in Leicester Cough Questionnaire (LCQ) total score *versus* a) baseline and b) placebo. Point estimates; vertical lines represent 90% credible limits. One-sided p-values are shown. Treatment time with each dose of eliapixant was 1 week. NS: nonsignificant.

TABLE 2 Summary of safety

	Placebo	Eliapixant				All treatments
		10 mg	50 mg	200 mg	750 mg	
Patients	40	39	39	39	39	40
Any AE	26 (65)	17 (44)	19 (49)	18 (46)	16 (41)	37 (93)
Severity of AE						
Mild	23 (58)	15 (38)	17 (44)	16 (41)	13 (33)	30 (75)
Moderate	2 (5)	2 (5)	2 (5)	2 (5)	3 (8)	6 (15)
Severe	1 (3)	0	0	0	0	1 (3)
Any study drug-related AE	5 (13)	0	8 (21)	8 (21)	5 (13)	14 (35)
Severity of study drug-related AE						
Mild	5 (13)	0	7 (18)	8 (21)	5 (13)	13 (33)
Moderate	0	0	1 (3)	0	0	1 (3)
Any AE leading to discontinuation of study drug	1 (3)	0	0	0	1 (3)	2 (5)
Any SAE	1 (3)	0	0	0	0	1 (3)

Data are presented as n or n (%). AE: adverse event; SAE: serious adverse event.

TABLE 3 Adverse events (AEs) reported in ⩾5% of patients in any group and taste-related AEs

	Placebo	Eliapixant				All treatments[#]
		10 mg	50 mg	200 mg	750 mg	
Patients	40	39	39	39	39	40
AEs reported in ⩾5% of patients in any group						
Headache	6 (15)	2 (5)	5 (13)	3 (8)	1 (3)	15 (38)
Dysgeusia	1 (3)	0	4 (10)	4 (10)	3 (8)	9 (23)
Fatigue	4 (10)	1 (3)	2 (5)	1 (3)	1 (3)	8 (20)
Diarrhoea	2 (5)	1 (3)	2 (5)	2 (5)	1 (3)	7 (18)
Nasopharyngitis	2 (5)	2 (5)	2 (5)	0	1 (3)	6 (15)
Upper respiratory tract infection	1 (3)	3 (8)	0	1 (3)	1 (3)	5 (13)
Cough	3 (8)	2 (5)	0	2 (5)	1 (3)	5 (13)
Dizziness	2 (5)	1 (3)	1 (3)	0	1 (3)	5 (13)
Nausea	1 (3)	1 (3)	1 (3)	1 (3)	0	4 (10)
Oropharyngeal pain	0	0	2 (5)	2 (5)	0	4 (10)
Decreased appetite	0	1 (3)	1 (3)	0	1 (3)	3 (8)
Nasal congestion	2 (5)	1 (3)	0	0	0	3 (8)
Dry throat	2 (5)	0	1 (3)	0	0	2 (5)
INR increased	1 (3)	0	0	1 (3)	0	2 (5)
Lethargy	0	0	0	2 (5)	0	2 (5)
Myalgia	1 (3)	0	1 (3)	0	0	2 (5)
Macular rash	0	1 (3)	0	0	1 (3)	2 (5)
Rhinorrhoea	2 (5)	0	0	0	0	2 (5)
Abdominal discomfort	0	1 (3)	0	1 (3)	0	2 (5)
Lower abdominal pain	1 (3)	0	0	0	1 (3)	2 (5)
Upper abdominal pain	0	1 (3)	0	1 (3)	0	2 (5)
Dry mouth	1 (3)	0	0	1 (3)	0	2 (5)
Dyspepsia	1 (3)	0	1 (3)	0	0	2 (5)
Oral paraesthesia	1 (3)	0	1 (3)	1 (3)	0	2 (5)
Vomiting	1 (3)	0	0	0	1 (3)	2 (5)
Feeling cold	1 (3)	1 (3)	0	0	0	2 (5)
Oral herpes	0	0	2 (5)	0	0	2 (5)
Urinary tract infection	1 (3)	0	0	0	1 (3)	2 (5)
Fall	2 (5)	0	0	0	0	2 (5)
Taste-related AEs[¶]						
Dysgeusia	1 (3)	0	4 (10)	4 (10)	3 (8)	9 (23)
Ageusia	0	0	0	1 (3)	0	1 (3)
Hypogeusia	0	0	0	1 (3)	0	1 (3)

Data are presented as n or n (%). INR: international normalised ratio. [#]: data in this column count the patient over all treatment periods (one patient who had an AE at two or more different doses was counted only once); [¶]: data are shown only for the dose at which the event first occurred, regardless of whether the event continued or recurred at subsequent doses.

eliapixant, with no dose relationship, and 3% of patients receiving placebo (table 3). All taste-related AEs were mild in severity. There was no relationship between taste-related AEs and the magnitude of cough frequency reduction (data not shown). All taste-related AEs were reversible: their duration was <30 days in nine patients, 41 days in one patient (dysgeusia) and 72 days in one patient (dysgeusia).

On the cumulative assessment, the incidence of taste-related AEs was 3% for placebo, and 5%, 10%, 15% and 21% for eliapixant 10, 50, 200 and 750 mg, respectively.

Pharmacokinetics

Plasma concentrations of eliapixant increased with dose in a nonlinear fashion (supplementary figure S4).

Discussion

This study investigated the efficacy, safety and tolerability of the highly selective P2X3 receptor antagonist eliapixant in patients with RCC. The demographics [30], baseline cough frequency and LCQ score were comparable to those reported elsewhere for patients with UCC [31], suggesting that the study population was typical of RCC patients seen in the clinic.

Eliapixant produced dose-dependent reductions in cough frequency and severity, and improvements in cough-related quality of life. The reduction in cough frequency appeared to reach a plateau at 200 mg, whereas the subjective end-points continued to improve at the 750 mg dose. While some patients had previously participated in clinical trials of gefapixant, this is unlikely to have substantially biased the results, as patients were required to have taken their last dose of prior medication at least 2 months before the first dose of study medication in the present study.

The changes in cough frequency and severity were seen after 1 week of each dose of eliapixant, even though the compound would have taken ∼5 days to reach steady-state plasma levels with the applied dosing regimen (Bayer, data on file). The sparse sampling conducted in the present study meant that no pharmacokinetic parameters could be calculated using noncompartmental methods. In part 1 of the study, in healthy volunteers (to be published separately) increases in plasma concentrations with increasing eliapixant dose were less than dose proportional. Peak plasma concentrations were reached 3–4 h after administration of the first and subsequent doses, and the terminal half-life ranged from 52 to 78 h. The 200 and 750 mg doses achieve plasma drug concentrations shown to produce P2X3 receptor occupancy >80% in pre-clinical and *in vitro* models: the concentration required to occupy 80% of P2X2/3 receptors is ∼20 times higher (Bayer, data on file). Pre-clinical data indicate that P2X3 receptor occupancy >80% is the expected relevant threshold for efficacy (Bayer, data on file).

The increases in LCQ score in the current study (1.09 and 1.53 points *versus* placebo at 200 and 750 mg, respectively) are close to the minimal clinically important difference for this measure, generally reported as 1.3 points [32–34] (although higher values have been suggested [33]). These results should be viewed with caution because the LCQ is a validated assessment of the impact of cough on quality of life during the preceding 14 days rather than the 1-week duration of treatment at each dose here, which may be too short to see substantial changes in quality of life. Other studies that used the LCQ typically involved treatment durations of 1–3 months [35–38].

In recent phase 3 trials, gefapixant 45 mg twice daily, which inhibits both P2X3 and P2X2/3 receptors, reduced awake cough frequency by 18% *versus* placebo at week 12 (COUGH-1) and by 16% *versus* placebo at week 24 (COUGH-2) [23]. The reductions in 24-h cough frequency *versus* placebo were 18% and 15%, respectively. These studies noted a large placebo effect, with a reduction in awake cough frequency by >50%. However, in a phase 2a trial of a similar scale and design to the current study, also in patients attending specialist clinics, gefapixant reduced awake cough frequency by up to 57% *versus* baseline [14]. The current results with a second P2X3 receptor antagonist, shown in pre-clinical studies to be highly selective for the P2X3 receptor (see earlier), suggest that P2X3 receptor antagonism is an important mechanism for the reduction of cough frequency and severity with this class of drugs. Comparisons across clinical trials of P2X3 receptor antagonists are hampered by differences in designs, patient populations and placebo effects. The efficacy of gefapixant may partly reflect a role for P2X2/3 receptor antagonism in antitussive efficacy, but it is also possible that taste-related AEs resulting from P2X2/3 blockade led patients to expect a benefit, which added as a component to P2X3-mediated efficacy. In future, comparative studies of different P2X3 antagonists of differing receptor specificity will be required to answer this question.

Dysgeusia was reported in 8–10% of patients receiving eliapixant, with no dose relationship. Importantly, all taste-related AEs were mild and no patient withdrew because of these events. The incidence of taste-related AEs was higher on the cumulative analysis, reaching 21% at the highest dose (750 mg); this may reflect accumulated events from preceding dosing periods rather than a dose relationship. Results in healthy volunteers have shown similar rates of these events with eliapixant and placebo (Bayer, data on file). Patients and healthy volunteers were advised of the possibility of taste-related AEs and this, combined with unblinding by the reduction of cough, may have influenced their perception of these events. It is difficult to say how prior participation in a P2X3 antagonist trial might have influenced reporting of AEs. While some patients might have reported taste AEs more readily because they had experienced them before, others might have been less likely to do so because they were already expecting them.

In phase 3 trials, taste-related AEs, mainly dysgeusia, were reported in 11–20% of patients receiving gefapixant 15 mg twice daily and 58–69% with 45 mg twice daily [23]. These AEs are believed to be related to antagonism of P2X2/3 receptors on gustatory afferents [39] as gefapixant has little selectivity for the P2X3 receptor over the P2X2/3 receptor [12]. Direct comparisons are difficult, but the apparent lower incidence of taste disturbances at therapeutic doses with eliapixant than with gefapixant suggests that reduction of these effects is related to specificity for P2X3 receptors over P2X2/3 receptors [40]. Eliapixant has a low time to peak plasma concentration, a long terminal half-life and low fluctuation of plasma levels at steady state (Bayer, data on file). These properties may improve the efficacy–tolerability balance by maintaining therapeutic concentrations throughout the dosing period while not approaching concentrations linked to taste side-effects.

Another P2X3 receptor antagonist, BLU-5937, showed promise in healthy subjects [41, 42]. The phase 2 study of this compound failed to achieve the primary end-point of a reduction in awake cough frequency [43]; a pre-specified subgroup analysis, however, demonstrated significant cough suppression. A fourth compound, S-6000918 (sivopixant), has reported encouraging results in RCC [29]. Comparisons across trials are problematic because of small patient numbers, differences in designs, treatment durations and patient populations, and the widely varying placebo effects between studies.

An important strength of the current study is the crossover design, in which each patient served as their own control for the objectively measured end-point. A crossover design was appropriate because RCC is a chronic, symptomatic condition and the effects of eliapixant were expected to be reversible, as observed with gefapixant [14]. The washout period far exceeded the half-life, reducing drug-related carryover effects. Moreover, the primary end-point was assessed based on repeated measurements *versus* baseline, which would be expected to eliminate carryover effects. Limitations included potential unblinding resulting from taste-related AEs (less than with gefapixant), the small sample size, and the limited duration of treatment and follow-up. A phase 2b trial of eliapixant has been designed to address some of these limitations.

Conclusions

The current study verifies that P2X3 receptor antagonism is an effective therapeutic pathway for the treatment of RCC. Eliapixant at doses of 200 and 750 mg significantly reduced cough frequency and severity, and was well tolerated. The study population was typical of patients with RCC [30] and therefore the findings are likely to be generalisable beyond clinical trial populations. Compared with gefapixant, eliapixant produced a lower rate of taste-related AEs, likely because of its greater selectivity for the P2X3 receptor. Further studies are required, but more selective P2X3 receptor antagonists such as eliapixant may be better tolerated than less selective drugs.

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This study is registered at ClinicalTrials.gov with identifier number NCT03310645. Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations and Pharmaceutical Research and Manufacturers of America principles for responsible clinical trial data sharing, pertaining to scope, time-point and process of data access. Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union as necessary for doing legitimate research. This commitment applies to data on

new medicines and indications that have been approved by the European Union and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to do further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsor's section of the portal. Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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