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Early View

Original article

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

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ABSTRACT 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.

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 endpoint was change in cough frequency assessed over 24 h (VitaloJAK). Primary safety endpoint was frequency and severity of adverse events (AEs).

Thirty-seven 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% confidence interval, 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.

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.

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Introduction

Chronic cough is generally defined as a cough lasting for 8 weeks or more [1, 2], and is estimated to affect approximately 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 adenosine triphosphate (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 Að 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 m^{-2}, diagnosed with RCC for ≥1 year, unresponsive to treatment according to the 2006 British Thoracic Society guideline 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 longer than 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 supplemental table 1.

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 mg, 25 mg 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 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 electrocardiogram 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) [25].

Outcomes

The primary efficacy endpoint was the change in cough frequency per hour, assessed objectively over 24-h periods using the VitaloJAK cough recorder (Vitalograph, Maids Moreton, UK) [26, 27]. 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 endpoints 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 endpoint 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 hours post-dose on Day 0, and at 0, 2, 4, 6, and 23.5 hours post-dose on Days 6, 13, and 20.

Study oversight and approvals

The protocol and all amendments were reviewed and approved by an ethics committee 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.

Role of the funding source

The study sponsor, Bayer AG, was responsible for study design, data collection, data analysis, data interpretation and study report writing. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit this paper for publication.

Randomisation, blinding and statistical techniques

Since the study was a proof of concept study, a Bayesian approach with non-informative 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) analysis of covariance on the primary endpoints, 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 carry-over 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 supplemental file 1.

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 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 1 patient withdrew for personal reasons. In total, therefore, 37 patients completed randomised treatment. All 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 (9 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 n=20	**Sequence B–A n=20**	**Total n=40**
Sex, n (%)			
Male	6 (30)	3 (15)	9 (23)
Female	14 (70)	17 (85)	31 (78)
Race, n (%)			
Black or African American	1 (5)	0	1 (3)
White	19 (95)	20 (100)	39 (98)
Age (years)			
Mean±SD	60.6±13.2	62.4±7.0	61.5±10.5
Range	20–76	50–75	20–76
BMI (kg m^{-2})			
Mean±SD	26.7±3.1	26.9±3.7	26.8±3.4
Smoking history, n (%)			
Never	14 (70)	11 (55)	25 (63)
Former	6 (30)	9 (45)	15 (38)
Prior medication*, n (%)	17 (85)	15 (75)	32 (80)
Geometric mean cough frequency per hour (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, 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)

*Any prior medication used within 4 weeks before the screening visit.

BMI: body mass index; CL: credible limit; LCQ: Leicester Cough Questionnaire; SD: standard deviation.

Efficacy

Cough frequency (measured over 24 hours) decreased by a mean of 17.4% *versus* baseline with placebo and by 9.4% to 38.1% *versus* baseline with eliapixant (supplemental tables 2 and 3; figure 3a). Placebo-corrected changes with eliapixant ranged from +9.5% to –25.0% (supplemental tables 2 and 3; 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 (supplemental tables 2 and 3; figure 3c). Placebo-corrected changes in awake cough frequency with eliapixant ranged from +5.2% to –26.1% (supplemental tables 2 and 3; 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 supplemental figure 1.

In a *post hoc* analysis the placebo adjustment as performed for trials of other P2X3 receptor antagonists [28], in which arithmetic rather than geometric means appear to have been used, was applied. In this analysis, cough frequency over 24 hours and awake cough frequency were reduced by 30.6% and 32.1% *versus* placebo, respectively, with the 750 mg dose (Supplemental figure 2).

Cough severity showed a dose-dependent reduction with eliapixant (supplemental tables 4 and 5; figure 4). Absolute cough severities are shown in supplemental figure 3.
Doses of eliapixant ≥50 mg increased LCQ (representing improvement) *versus* baseline and *versus* placebo (supplemental tables 6 and 7; figure 5).

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%) (supplemental table 8). 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 above were reported (data not shown).

TABLE 2 Summary of safety

	Placebo	**Eliapixant**				**All**
	n=40	**10 mg**	**50 mg**	**200 mg**	**750 mg**	**treatments**
		n=39	**n=39**	**n=39**	**n=39**	**n=40**
Any AE, n (%)	26 (65)	17 (44)	19 (49)	18 (46)	16 (41)	37 (93)
Severity of AE, n (%)						
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, n (%)	5 (13)	0	8 (21)	8 (21)	5 (13)	14 (35)
Severity of study drug-related AE, n (%)						
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, n (%)	1 (3)	0	0	0	1 (3)	2 (5)
Any SAE, n (%)	1 (3)	0	0	0	0	1 (3)

AE: adverse event; SAE: serious adverse event.

The most frequently reported AEs overall were headache, dysgeusia, fatigue and diarrhoea (table 3a). Dysgeusia, in terms of the first occurrence of the event, was reported in 8−10% of patients receiving eliapixant, with no dose relationship, and 3% of patients receiving placebo (table 3b). 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 mg, 50 mg, 200 mg and 750 mg, respectively.

TABLE 3 a) AEs reported in ≥5% of patients in any group. b) Taste-related AEs

a) AEs, n (%)	Placebo	Eliapixant				All treatments*
	n=40	10 mg	50 mg	200 mg	750 mg	n=40
		n=39	n=39	n=39	n=39	
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)

b) 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 in this column count the patient over all treatment periods; 1 patient who had an AE at ≥2 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. AE: adverse event; INR: international normalised ratio.

Pharmacokinetics

Plasma concentrations of eliapixant increased with dose in a non-linear fashion (supplemental figure 4).

Discussion

This study investigated the efficacy, safety and tolerability of the highly selective P2X3 receptor antagonist eliapixant in patients with RCC. The demographics [29], baseline cough frequency and LCQ were comparable to those reported elsewhere for patients with UCC, [30] 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 endpoints 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 approximately 5 days to reach steady-state plasma levels with the applied dosing regimen (Bayer AG, data on file). The sparse sampling conducted in the present study meant that no pharmacokinetic parameters could be calculated using non-compartmental 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 hours after administration of the first and subsequent doses, and the terminal half-life ranged from 52 to 78 hours. The 200 mg and 750 mg doses achieve plasma drug concentrations shown to produce P2X3 receptor occupancy >80% in preclinical and *in vitro* models: the concentration required to occupy 80% of P2X2/3 receptors is approximately 20 times higher (Bayer AG, data on file). Preclinical data indicate that P2X3 receptor occupancy >80% is the expected relevant threshold for efficacy (Bayer AG, data on file).

The increases in LCQ in the current study (1.09 and 1.53 points *versus* placebo at 200 mg and 750 mg, respectively) are close to the minimal clinically important difference for this measure, generally reported as 1.3 [31-33] (although higher values have been suggested) [32]. These results should be viewed with caution because the LCQ is a validated assessment of the impact of cough on QoL 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 [34-37].

In recent Phase 3 trials gefapixant 45 mg twice daily (BD), 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-hour cough frequency *versus* placebo were 18% and 15%, respectively. These studies noted a large placebo effect, with a reduction in awake cough frequency by over 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 preclinical studies to be highly selective for the P2X3 receptor (see above), 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 AG, 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 BD and 58–69% with 45 mg BD[23]. These AEs are believed to be related to antagonism of P2X2/3 receptors on gustatory afferents [38] 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 [39]. Eliapixant has a low time to peak plasma concentration, a long terminal half-life, and low fluctuation of plasma levels at steady state (Bayer AG, 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 [40, 41]. The Phase 2 study of this compound failed to achieve the primary endpoint of a reduction in awake cough frequency [42]; a pre-specified subgroup analysis, however, demonstrated significant cough suppression. A fourth compound − S-6000918 − has reported encouraging results in RCC [28]. Comparisons across trials are problematic because of small patient numbers, differences in designs, treatment durations, 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 endpoint. 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 carry-over effects. Moreover, the primary endpoint was assessed based on repeated measurements *versus* baseline, which would be expected to eliminate carry-over 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.

Conclusion

The current study verifies that P2X3 receptor antagonism is an effective therapeutic pathway for the treatment of RCC. Eliapixant at doses of 200 mg and 750 mg significantly reduced cough frequency and severity and was well tolerated. The study population was typical of patients with RCC [29] 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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Figure Legends

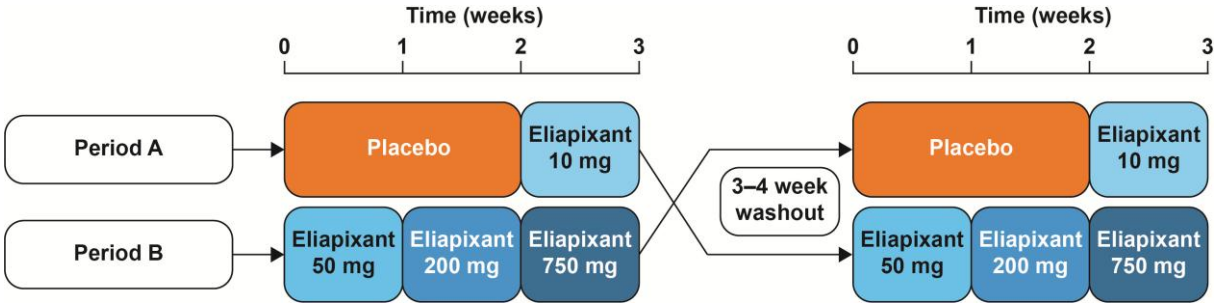
FIGURE 1 Study design.

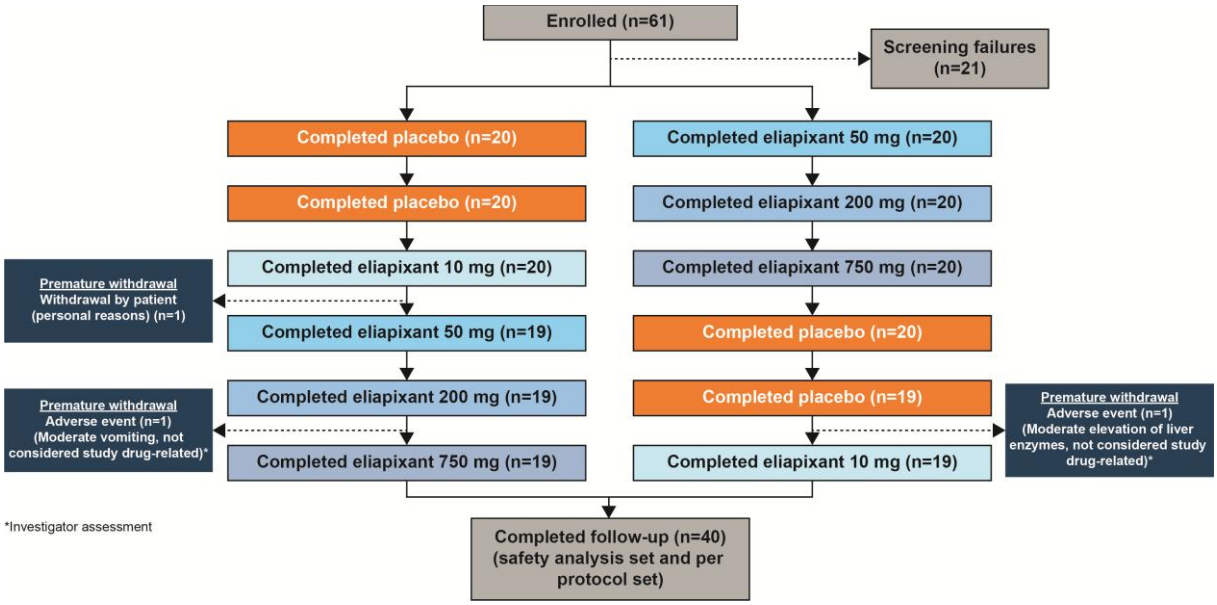
FIGURE 2 Patient disposition.

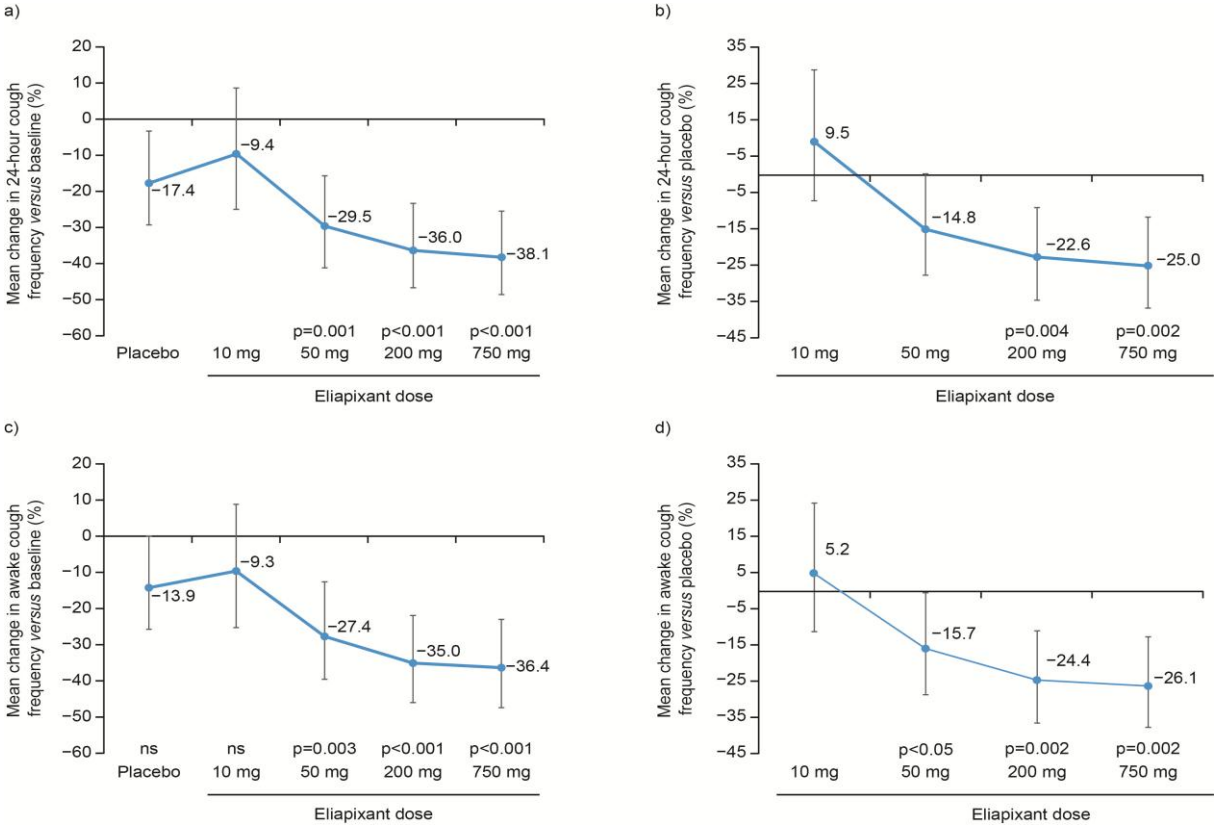
FIGURE 3 Mean changes in cough frequency (measured over 24 hours) *versus* baseline (3a) and *versus* placebo (3b). Data for awake cough frequency are shown in panels c and d. Bayesian mixed model analysis (n=40); vertical bars represent the 90% credible limits. Treatment time with each dose of eliapixant was 1 week.

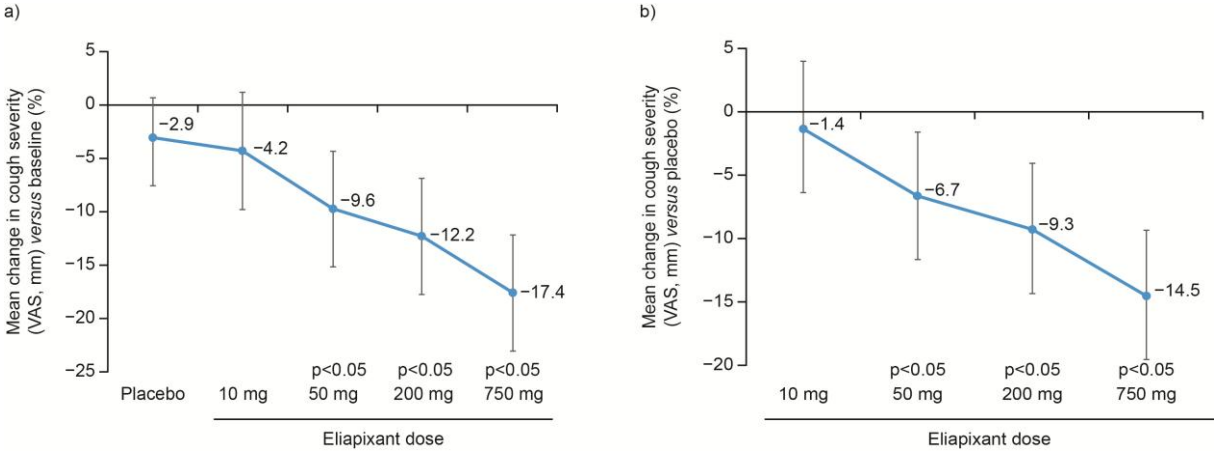
FIGURE 4 Mean changes in patient-reported cough severity *versus* baseline (a) and *versus* placebo (b). Point estimates; vertical lines represent 90% credible limits. One-sided p-values are shown. Treatment time with each dose of eliapixant was 1 week. VAS: visual analogue scale.

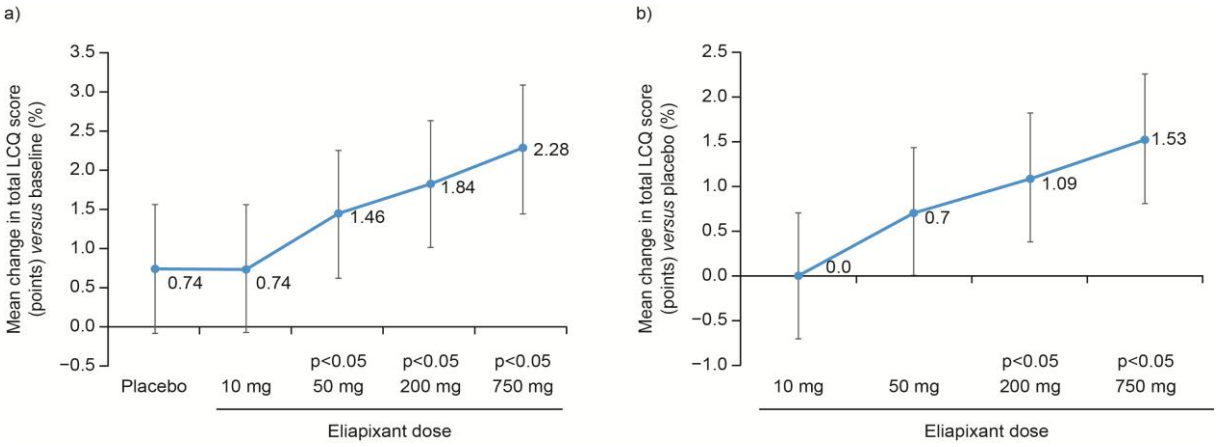
FIGURE 5 Mean changes in total LCQ score *versus* baseline (a) and *versus* placebo (b) LCQ: Leicester Cough Questionnaire. Point estimates; vertical lines represent 90% credible limits. One-sided p-values are shown. Treatment time with each dose of eliapixant was 1 week.


Time (weeks)
0
1
2
3
Time (weeks)
0
1
2
3
Period A
Placebo
Eliapixant 10 mg
Period B
Eliapixant 50 mg
Eliapixant 200 mg
Eliapixant 750 mg
3–4 week washout
Placebo
Eliapixant 10 mg
Eliapixant 50 mg
Eliapixant 200 mg
Eliapixant 750 mg


Enrolled (n=61)
Screening failures (n=21)
Completed placebo (n=20)
Completed placebo (n=20)
Completed eliapixant 10 mg (n=20)
Completed eliapixant 50 mg (n=19)
Completed eliapixant 200 mg (n=19)
Completed eliapixant 750 mg (n=19)
Completed eliapixant 50 mg (n=20)
Completed eliapixant 200 mg (n=20)
Completed eliapixant 750 mg (n=20)
Completed placebo (n=20)
Completed placebo (n=19)
Completed eliapixant 10 mg (n=19)
Premature withdrawal
Withdrawal by patient (personal reasons) (n=1)
Premature withdrawal
Adverse event (n=1)
(Moderate vomiting, not considered study drug-related)*
Premature withdrawal
Adverse event (n=1)
(Moderate elevation of liver enzymes, not considered study drug-related)*
*Investigator assessment
Completed follow-up (n=40) (safety analysis set and per protocol set)


a)
Mean change in 24-hour cough frequency *versus* baseline (%)
20
10
0
−10
−20
−30
−40
−50
−60
−17.4
−9.4
−29.5
−36.0
−38.1
Placebo
10 mg
p=0.001
50 mg
p<0.001
200 mg
p<0.001
750 mg
Eliapixant dose
b)
Mean change in 24-hour cough frequency *versus* placebo (%)
35
25
15
−5
−5
−15
−25
−35
−45
9.5
−14.8
−22.6
−25.0
10 mg
50 mg
p=0.004
200 mg
p=0.002
750 mg
Eliapixant dose
c)
Mean change in awake cough frequency *versus* baseline (%)
20
10
0
−10
−20
−30
−40
−50
−60
−13.9
−9.3
−27.4
−35.0
−36.4
ns
Placebo
ns
10 mg
p=0.003
50 mg
p<0.001
200 mg
p<0.001
750 mg
Eliapixant dose
d)
Mean change in awake cough frequency *versus* placebo (%)
35
25
15
5
−5
−15
−25
−35
−45
5.2
−15.7
−24.4
−26.1
10 mg
p<0.05
50 mg
p=0.002
200 mg
p=0.002
750 mg
Eliapixant dose


a)
Mean change in cough severity (VAS, mm) versus baseline (%)
5
0
−5
−10
−15
−20
−25
−2.9
−4.2
−9.6
−12.2
−17.4
Placebo
10 mg
p<0.05 50 mg
p<0.05 200 mg
p<0.05 750 mg
Eliapixant dose
b)
Mean change in cough severity (VAS, mm) versus placebo (%)
5
0
−5
−10
−15
−20
−1.4
−6.7
−9.3
−14.5
10 mg
p<0.05 50 mg
p<0.05 200 mg
p<0.05 750 mg
Eliapixant dose


a)
Mean change in total LCQ score (points) versus baseline (%)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
0.74
0.74
1.46
1.84
2.28
Placebo
10 mg
p<0.05 50 mg
p<0.05 200 mg
p<0.05 750 mg
Eliapixant dose
b)
Mean change in total LCQ score (points) versus placebo (%)
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
0.0
0.7
1.09
1.53
10 mg
50 mg
p<0.05 200 mg
p<0.05 750 mg
Eliapixant dose

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

Alyn Morice, Jaclyn A Smith, Lorcan McGarvey, Surinder S Birring, Sean M Parker, Alice Turner, Thomas Hummel, Isabella Gashaw, Lueder Fels, Stefan Klein, Klaus Francke and Christian Friedrich
For author affiliations please see the main paper.

SUPPLEMENTAL FILE 1

Randomisation and blinding

At the beginning of the first treatment period, participants who met the entry criteria were assigned sequentially to a unique randomisation number in ascending order. Randomisation number and allocation to one of the treatment sequences was assigned by a representative of the sponsor using the computer-generated list and was requested by each study site electronically. The study was double-blind, with investigators and patients (and site staff) blinded to the treatment. To ensure blinding, tablet formulations for each dose strength of active product and placebo were identical in size, shape, colour and smell. The packaging and labelling were designed to maintain blinding to site staff and patients, and the number and appearance of tablets for each treatment planned was identical for corresponding weeks of each treatment period.

Statistical analysis

The sample size was based on three assumptions: that improvement in 24-h cough frequency *versus* placebo with eliapixant would exceed 40% with the highest dose; that the overall coefficient of variation (CV) for every treatment period would be in the range 0.7–0.9; and that within-subject CV would be 50%. A sample size of 36 completers (18 per arm) was considered sufficient to achieve 80% power for demonstrating with a >85% level of proof that in the highest dose arm the improvement *versus* placebo exceeded 40%. To account for a dropout rate of about 10%, 40 patients were randomised.

Data from all patients randomised were used for subject validity, primary reasons for exclusion from analysis, patient disposition, end of study medication and data relating to patients prematurely breaking the treatment code. All participants who received at least one dose of study medication (eliapixant or placebo) were included in the safety analysis set. Analyses of efficacy and pharmacokinetics were conducted on the per protocol analysis set, which consisted of all patients who completed the study without validity findings. Pharmacokinetic results were presented by

plotting plasma concentration–time profiles, with no formal analysis of pharmacokinetic parameters. Missing data were not replaced. Logarithmized Ratios to baseline were analysed for cough count data, whereas for the other efficacy data the differences to baseline were analysed, using the following model:

$X_{itk} = S_i + \beta BL_{it} + \mu_{tk} + \varepsilon_{itk}$, where

X_{itk} is the measurement for patient i within sequence group k at time point t,

S_i is a $N(0;\tau)$ distributed subject effect for patient i,

BL_{it} is the baseline for subject i at time point t,

μ_{tk} is the mean change to baseline at time point t for sequence group k, and

ε_{itk} is a normally distributed error variable.

Changes vs placebo within dose d were determined using suitable contrast estimatesC_d on the parameters μ_{tk} , ie

$C_d = \hat{\mu}_d - \hat{\mu}_{plc}$, where

$\hat{\mu}_d$ is the estimate for the mean change to baseline at dose d (ie: mean of the model parameters μ_{tk} when dose d was administered), and

$\hat{\mu}_{plc}$ is the estimate for the mean change to baseline for placebo (ie the mean of the model parameters μ_{tk}.when placebo was administered).

For cough counts, the exponentialized values of C_d, $\hat{\mu}_d$, and $\hat{\mu}_{plc}$ were reported, in order to get estimates for ratio to placebo or baseline, respectively.

Statistical analysis was performed using SAS version 9.4 software. Summary statistics are presented per dose for patients treated with eliapixant and pooled for all patients who received placebo. All analyses were descriptive and exploratory: no confirmatory statistical analysis or interim analyses were performed.

SUPPLEMENTAL TABLE 1 Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
1. Signed informed-consent form before any study-specific tests or procedures were performed 2. Age >18 years at the first screening visit 3. Body mass index >18 kg m^{-2} and <35 kg m^{-2}. 4. RCC for at ≥1 year that has been shown to be unresponsive to treatment of cough according to the 2006 British Thoracic Society guidelines 5. Score of >40 mm on the cough severity visual analogue scale at screening. 6. For male patients – Male patients who are sexually active and have not been surgically sterilised had to agree to use two reliable and acceptable methods of contraception simultaneously (one method used by the study patient and one method used by the partner) during the study and for 90 days after receiving the investigational medicinal product and not to act as sperm donor for 90 days after dosing Female patients: – Confirmed post-menopausal woman (defined as exhibiting spontaneous amenorrhoea for ≥12 months before screening or as exhibiting spontaneous amenorrhoea for 6 months before screening with documented serum follicle-stimulating hormone levels >40 mIU mL^{-1}); or – Woman without childbearing potential	*Medical and surgical history* 1. FEV_1 or FVC <60% of predicted normal, at screening 2. History of upper or lower respiratory tract infection or recent significant change in pulmonary status within the 4 weeks before baseline visit 3. Severe renal impairment 4. Moderate or severe liver impairment 5. Severe cardiovascular diseases *Medication, drug use and special behavioural patterns* 6. Current smoking habit or history of smoking within the 6 months before the screening visit 7. History of smoking (at any time) for >20 pack-years in total (20 cigarettes per pack) 8. History of opioid use within the week before the screening visit 9. Use of any systemic or topically active drug that might have influenced the pharmacokinetics of the study drug within the 14 days before first study drug administration or during the trial until the follow-up examination 10. Regular use of any systemic or topically active drug that modulates cough – such as acetylcholine esterase

based on surgical treatment ≥6 weeks before screening such as bilateral tubal ligation, bilateral oophorectomy with or without hysterectomy (documented by medical report verification); or

- Woman of childbearing potential who agreed to use two reliable and acceptable methods of contraception simultaneously (one method used by the study patient and one method used by the partner) during the study and for ≥10 days after the last dose

7. Ability to understand and follow study-related instructions
8. Previous use of P2X3 antagonists was permitted

inhibitors, opioids, pregabalin or gabapentin – within the 14 days before first study drug administration or during the trial until the follow-up examination

11. History of concurrent malignancy or recurrence of malignancy within the 2 years before screening (this does not apply to patients with <3 excised basal cell carcinomas)

ECG, blood pressure, heart rate

12. Systolic blood pressure <100 mmHg or >160 mmHg
13. Diastolic blood pressure <60 mmHg or >100 mmHg
14. Heart rate <50 beats min^{-1} or >95 beats min^{-1}
15. Clinically significant abnormal electrocardiogram at screening (especially second- or third-degree atrioventricular block or hints or evidence for long QT syndrome).

Laboratory examination

16. Clinically relevant deviations of the screened laboratory values from their respective reference ranges (especially persistent elevation of liver enzymes >2× upper limit of normal for alanine aminotransferase and/or aspartate transaminase and/or >1.5× upper limit of normal for bilirubin)
17. Positive results for hepatitis B virus

	surface antigen, hepatitis C virus antibodies or human immune deficiency virus antibodies. Other 18. Current pregnancy or breast-feeding 19. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that might have increased the risk associated with participation in the trial or administration of the investigational product or might have interfered with the interpretation of trial results and, in the judgement of the investigator or the sponsor, would make the subject inappropriate for entry into this trial 20. Previous assignment to treatment (*i.e.* randomisation) during this study

ECG: electrocardiogram; FEV_1: forced expiratory volume in the first one second; FVC: forced vital capacity of the lungs.

SUPPLEMENTAL TABLE 2 Summary statistics for a) total, b) awake, and c) asleep cough counts measured during 1-day periods

a)

Treatment	N	**Geometric mean (SD, CV%)**	**Arithmetic mean (SD, CV%)**	**Median (range)**
Baseline (period A)	40	25.5 (2.5, 112.9)	37.4 (40.9, 109.4)	24.0 (2.6–234.0)
Placebo (Day 7)	40	20.0 (2.7, 127.1)	30.6 (35.7, 116.6)	23.1 (1.7–204.3)
Placebo (Day 14)	40	22.6 (2.5, 112.6)	32.1 (31.0, 96.7)	22.8 (1.0–167.1)
Eliapixant 10 mg	39	22.8 (2.6, 123.9)	34.5 (39.3, 113.8)	24.1 (0.8–212.1)
Baseline (Period B)	39	26.6 (2.5, 112.6)	42.3 (65.4, 154.6)	24.7 (3.2–405.4)
Eliapixant 50 mg	39	18.8 (2.8, 139.3)	31.4 (44.8, 142.6)	18.3 (0.5–265.9)
Eliapixant 200 mg	39	17.1 (2.6, 124.5)	24.5 (21.7, 88.5)	20.1 (0.5–100.1)
Eliapixant 750 mg	38	16.6 (2.4, 108.1)	24.6 (31.6, 128.5)	14.3 (1.5–184.6)

b)

Treatment	N	**Geometric mean (SD, CV%)**	**Arithmetic mean (SD, CV%)**	**Median (range)**
Baseline (period A)	40	33.3 (2.5, 114.3)	49.6 (57.1, 115.2)	29.2 (3.9–332.6)
Placebo (Day 7)	40	27.6 (2.7, 128.1)	43.1 (52.3, 121.5)	33.5 (2.4–300.1)
Placebo (Day 14)	40	30.5 (2.5, 111.4)	43.3 (42.3, 97.7)	32.4 (1.5–232.8)
Eliapixant 10 mg	39	30.0 (2.7, 130.1)	47.1 (55.9, 118.6)	32.7 (1.1–288.6)
Baseline (Period B)	39	35.4 (2.5, 115.6)	58.1 (95.6, 164.5)	35.0 (4.0–595.7)
Eliapixant 50 mg	39	25.6 (2.8, 140.6)	43.9 (65.0, 148.2)	25.6 (0.8–384.8)
Eliapixant 200 mg	39	22.9 (2.7, 131.4)	33.9 (31.3, 92.4)	27.0 (0.4–152.8)
Eliapixant 750 mg	38	22.6 (2,4, 109.3)	34.4 (47.0, 136.6)	19.9 (2.4–272.7)

c)

Treatment	N	**Geometric mean (SD, CV%)**	**Arithmetic mean (SD, CV%)**	**Median (range)**
Baseline (period A)	40	2.5 (3.9, 230.5)	6.1 (11.3, 184.0)	1.36 (0.0–54.1)
Placebo (Day 7)	40	2.3 (3.7, 214.0)	5.0 (8.6, 171.5)	1.2 (0.0–37.0)
Placebo (Day 14)	40	2.3 (3.7, 214.1)	5.2 (9.7, 187.4)	1.6 (0.0–51.1)
Eliapixant 10 mg	39	2.7 (3.9, 236.6)	6.0 (10.1, 167.4)	2.6 (0.0–45.7)
Baseline (Period B)	39	2.1 (3.5, 196.7)	4.1 (6.7, 162.5)	1.4 (0.0–34.5)

Eliapixant 50 mg	39	1.9 (3.8, 224.8)	4.1 (6.4, 155.1)	0.6 (0.0–24.1)
Eliapixant 200 mg	39	2.4 (3.6, 201.7)	4.8 (6.8, 142.5)	1.5 (0.0–27.7)
Eliapixant 750 mg	38	2.0 (3.5, 191.2)	4.0 (6.9, 173.8)	1.1 (0.0–35.8)

CV: coefficient of variation; SD: standard deviation.

SUPPLEMENTAL TABLE 3 Mean relative changes in cough frequency *versus* placebo and baseline

Analysis group	Mean cough frequency (90% CL)	Mean relative change *versus* placebo, % (90% CL)	p-value
24-h			
Placebo	21.4 (18.4, 25.1)	– (–, –)	–
Eliapixant 10 mg	23.5 (19.5, 28.1)	9.5 (29.0, −7.0)	0.818
Eliapixant 50 mg	18.3 (15.3, 21.9)	−14.8 (0.4, −27.6)	0.054
Eliapixant 200 mg	16.6 (13.9, 19.9)	−22.6 (−8.9, −34.4)	0.004
Eliapixant 750 mg	16.0 (13.4, 19.4)	−25.0 (−11.5, −36.5)	0.002
Awake			
Placebo	29.4 (25.1, 34.5)	– (–, –)	–
Eliapixant 10 mg	30.9 (25.5, 37.2)	5.2 (24.3, –11.0)	0.692
Eliapixant 50 mg	24.8 (20.7, 29.8)	−15.7 (0.3, −28.5)	0.046
Eliapixant 200 mg	22.2 (18.5, 26.7)	−24.4 (−10.8, −36.2)	0.002
Eliapixant 750 mg	21.7 (18.0, 26.3)	−26.1 (−12.5, −37.6)	0.002
Analysis group	**Ratio to baseline, (%) (90% CL)**	**Mean relative change *versus* baseline, % (90% CL)**	**p-value**
24-h			
Placebo	82.6 (70.9, 96.7)	−17.4 (−3.3, −29.1)	0.025
Eliapixant 10 mg	90.6 (75.1, 108.6)	−9.4 (8.6, −24.9)	0.182
Eliapixant 50 mg	70.5 (59.0, 84.4)	−29.5 (−15.6, −41.0)	0.001
Eliapixant 200 mg	64.0 (53.5, 76.8)	−36.0 (−23.2, −46.5)	<0.001
Eliapixant 750 mg	61.9 (51.6, 74.7)	−38.1 (−25.3, −48.4)	<0.001
Awake			
Placebo	86.1 (73.5, 101.0)	−13.9 (1.0, −26.5)	0.063
Eliapixant 10 mg	90.7 (74.8, 109.0)	−9.3 (9.0, −25.2)	0.189
Eliapixant 50 mg	72.6 (60.6, 87.4)	−27.4 (−12.6, −39.4)	0.003
Eliapixant 200 mg	65.0 (54.2, 78.3)	−35.0 (−21.7, −45.8)	<0.001
Eliapixant 750 mg	63.6 (52.8, 77.1)	−36.4 (−22.9, −47.2)	<0.001

Bayesian mixed model (per protocol set, n=40). CL: credible limits. Treatment time with each dose of eliapixant was 1 week.

SUPPLEMENTAL TABLE 4 Summary statistics for cough severity and changes from baseline

Treatment	**Time**	N	**Cough severity (VAS)**		**Change from baseline**	
			Mean (SD)	**Median (range)**	**Mean (SD)**	**Median (range)**
Screening	–	40	74.3 (13.0)	76.0 (40–97)	–	–
Pre-dose (period A)	Day 1	40	70.6 (17.3)	72.5 (12–99)	–	–
Placebo	Day 7	39	70.1 (16.9)	74.0 (29–96)	–0.6 (12.7)	1.0 (–44 to 29)
Placebo	Day 14	39	66.4 (19.1)	69.0 (17–99)	–4.1 (16.2)	–4.0 (–56 to 24)
Eliapixant 10 mg	Day 21	38	67.2 (21.8)	76.0 (7–98)	–3.4 (22.6)	–0.5 (–66 to 37)
Pre-dose (Period B)	Day 1	39	71.4 (16.3)	73.0 (21–97)	–	–
Eliapixant 50 mg	Day 7	39	61.0 (21.4)	64.0 (3–96)	–10.4 (21.6)	–5.0 (–72 to 26)
Eliapixant 200 mg	Day 14	39	58.5 (23.2)	58.0 (5–98)	–12.9 (27.9)	–10.0 (–91 to 59)
Eliapixant 750 mg	Day 21	38	53.0 (23.3)	59.0 (7–98)	–17.9 (29.0)	–10.5 (–85 to 56)
Follow-up	–	40	63.5 (22.9)	72.5 (14–97)	–7.0 (22.5)	–1.5 (–76 to 37)

Data are expressed as mean (standard deviation).

VAS: visual analogue scale.

Baseline: last measurement before treatment.

No treatment was being received at follow-up.

SUPPLEMENTAL TABLE 5 Changes in cough severity *versus* placebo and baseline

Analysis group	**Change from baseline (90% CL)**	**p-value**	**Change *versus* placebo (90% CL)**	**p-value**
Placebo	2.90 (−1.71, 7.46)	NS	– (–, –)	–
Eliapixant 10 mg	4.20 (−1.30, 9.65)	NS	1.35 (−3.92, 6.43)	NS
Eliapixant 50 mg	9.58 (4.25, 15.06)	<0.05	6.68 (1.67, 11.73)	<0.05
Eliapixant 200 mg	12.17 (6.79, 17.61)	<0.05	9.28 (4.12, 14.37)	<0.05
Eliapixant 750 mg	17.41 (12.06, 22.90)	<0.05	14.51 (9.42, 19.62)	<0.05

Data are point estimates (per protocol set, n=40). CL: credible limits; NS: not significant. Treatment time with each dose of eliapixant was 1 week.

SUPPLEMENTAL TABLE 6 Summary statistics for LCQ total score and changes from baseline

Treatment	N	**Time**	**LCQ total score**		**Change from baseline**	
			Mean (SD)	**Median (range)**	**Mean (SD)**	**Median (range)**
Pre-dose (period A)	40	Day −1	11.54 (3.51)	11.16 (5.50–19.07)	–	–
Placebo	39	Day 7	11.98 (3.49)	11.54 (4.95–20.36)	0.35 (1.95)	0.79 (–8.95 to 3.61)
Placebo	39	Day 14	12.25 (3.06)	12.21 (6.23–18.14)	0.56 (2.61)	0.79 (–8.59 to 9.82)
Eliapixant 10 mg	39	Day 21	12.25 (3.18)	12.02 (5.36–18.57)	0.55 (3.11)	1.04 (–9.63 to 9.57)
Pre-dose (Period B)	39	Day −1	11.10 (3.20)	11.45 (4.82–18.18)	–	–
Eliapixant 50 mg	39	Day 7	12.84 (3.26)	13.23 (5.59–19.07)	1.75 (2.82)	1.20 (–2.38 to 13.13)
Eliapixant 200 mg	39	Day 14	13.23 (3.82)	14.14 (5.98–20.25)	2.13 (3.39)	1.18 (–3.30 to 11.61)
Eliapixant 750 mg	38	Day 21	13.69 (3.89)	13.96 (5.83–20.09)	2.54 (3.28)	1.38 (–1.95 to 11.21)

Data are expressed as mean (standard deviation).

LCQ: Leicester Cough Questionnaire.

Baseline: last measurement before treatment.

SUPPLEMENTAL TABLE 7 Changes in LCQ total score *versus* placebo and baseline

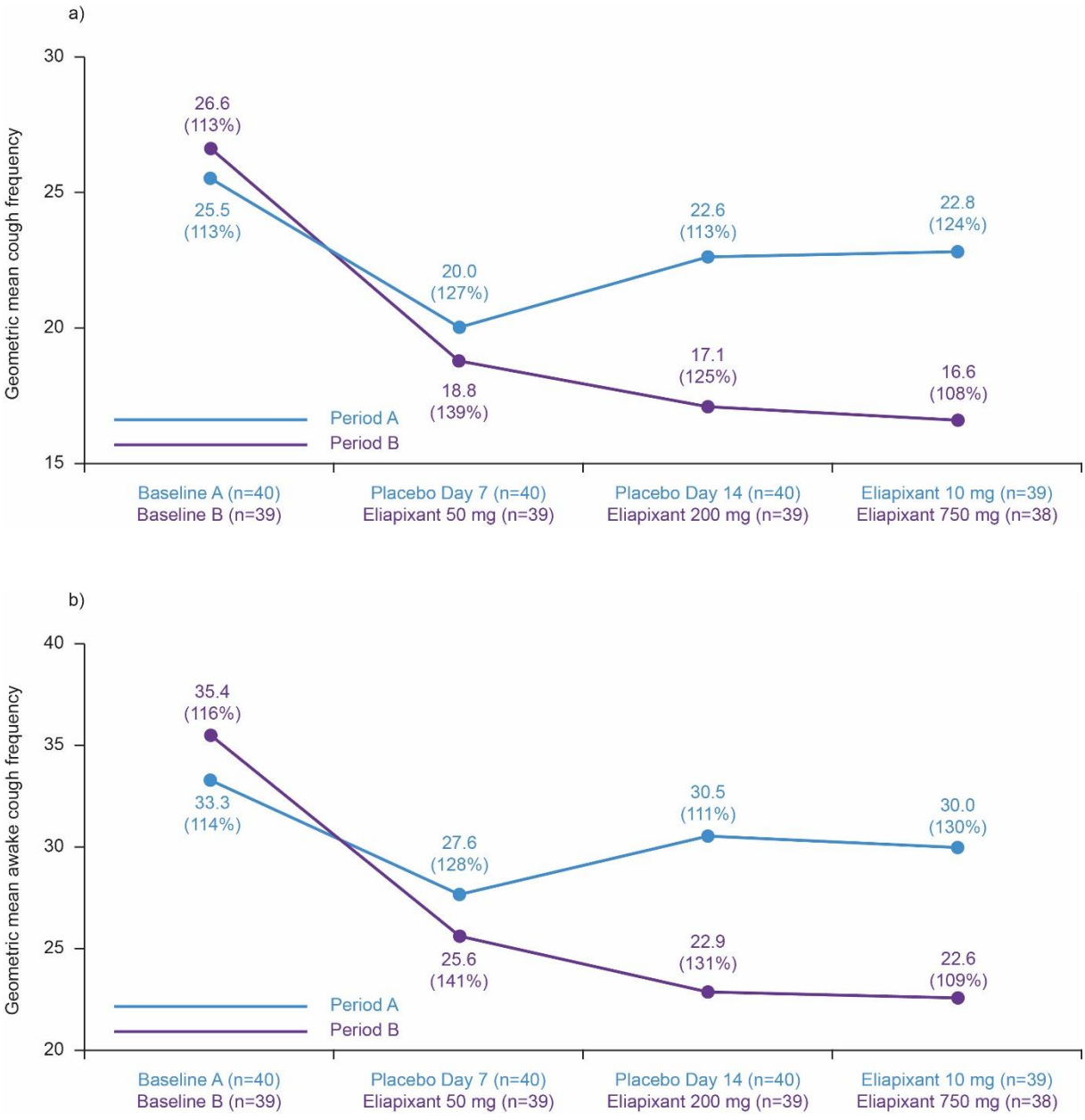
Analysis group	**Change from baseline (90% CL)**	**p-value**	**Change *versus* placebo (90% CL)**	**p-value**
Placebo	0.74 (1.56, −0.08)	NS	– (–, –)	–
Eliapixant 10 mg	0.74 (1.56, −0.07)	NS	0.00 (0.70, −0.71)	NS
Eliapixant 50 mg	1.46 (2.25, 0.62)	<0.05	0.70 (1.43, 0.00)	NS
Eliapixant 200 mg	1.84 (2.64, 1.02)	<0.05	1.09 (1.82, 0.38)	<0.05
Eliapixant 750 mg	2.28 (3.09, 1.45)	<0.05	1.53 (2.25, 0.81)	<0.05

Data are point estimates (per protocol set, n=40). CL: credible limits; NS: not significant. Treatment time with each dose of eliapixant was 1 week.

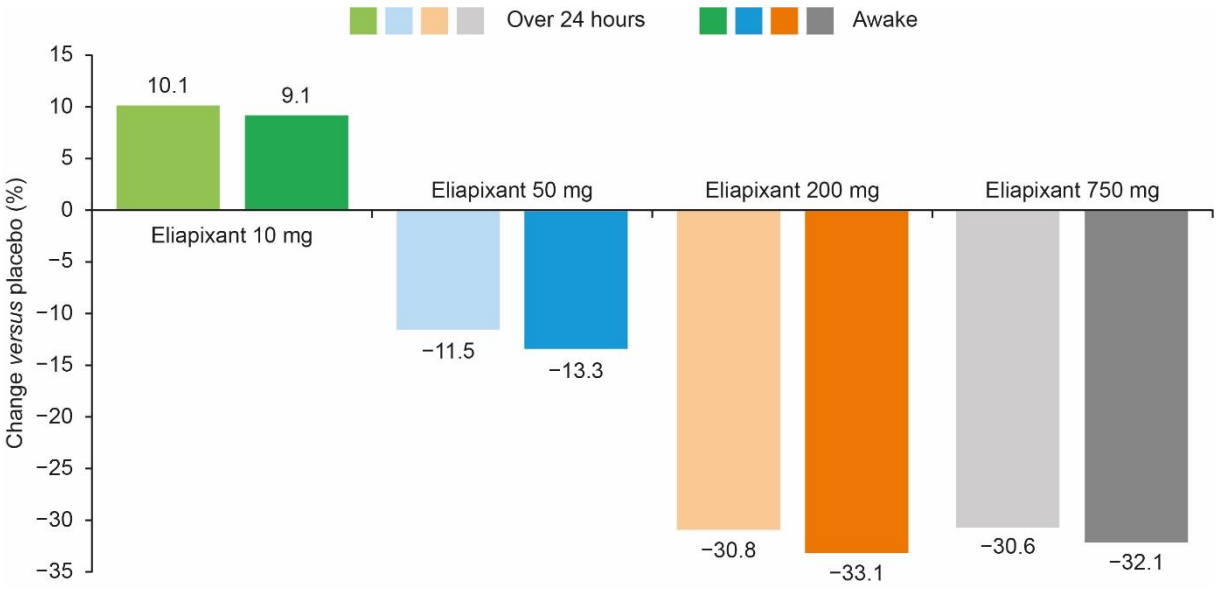
SUPPLEMENTAL TABLE 8 AEs considered by the investigator to be related to study drug

AE, n (%)	**Placebo**	**Eliapixant**				**All treatments**
	n=40	**10 mg**	**50 mg**	**200 mg**	**750 mg**	**n=40**
		n=39	**n=39**	**n=39**	**n=39**	
Any	*5 (13)*	*0*	*8 (21)*	*8 (21)*	*5 (13)*	*14 (35)*
Dysgeusia	1 (3)	0	4 (10)	4 (10)	3 (8)	9 (23)
Headache	2 (5)	0	1 (3)	1 (3)	0	4 (10)
Oral paraesthesia	1 (3)	0	1 (3)	1 (3)	0	2 (5)
Ageusia	0	0	0	1 (3)	0	1 (3)
Abdominal discomfort	0	0	0	1 (3)	0	1 (3)
Blood creatine phosphokinase increased	0	0	0	0	1 (3)	1 (3)
Decreased appetite	0	0	0	0	1 (3)	1 (3)
Diarrhoea	0	0	1 (3)	0	0	1 (3)
Dry mouth	0	0	0	1 (3)	0	1 (3)
Extrasystoles	1 (3)	0	0	0	0	1 (3)
Flatulence	0	0	1 (3)	0	0	1 (3)
Frequent bowel movements	0	0	1 (3)	0	0	1 (3)
Hypogeusia	0	0	0	1 (3)	0	1 (3)
International normalised ratio increased	0	0	0	1 (3)	0	1 (3)
Rhinitis	0	0	1 (3)	1 (3)	0	1 (3)
Rhinorrhoea	1 (3)	0	0	0	0	1 (3)
Supraventricular extrasystoles	1 (3)	0	0	0	0	1 (3)

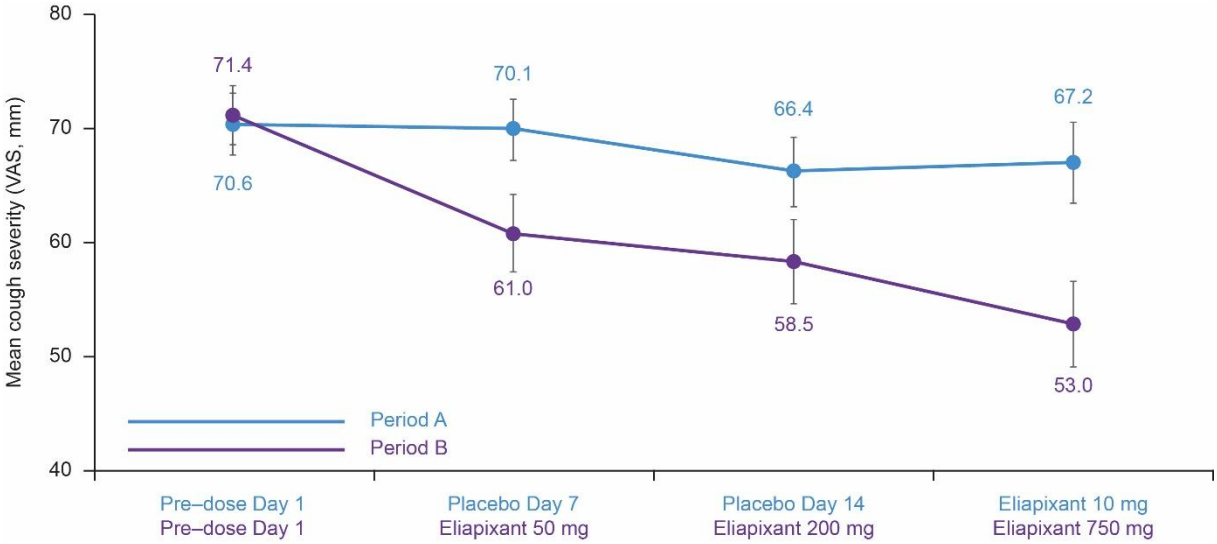
AE: adverse event.



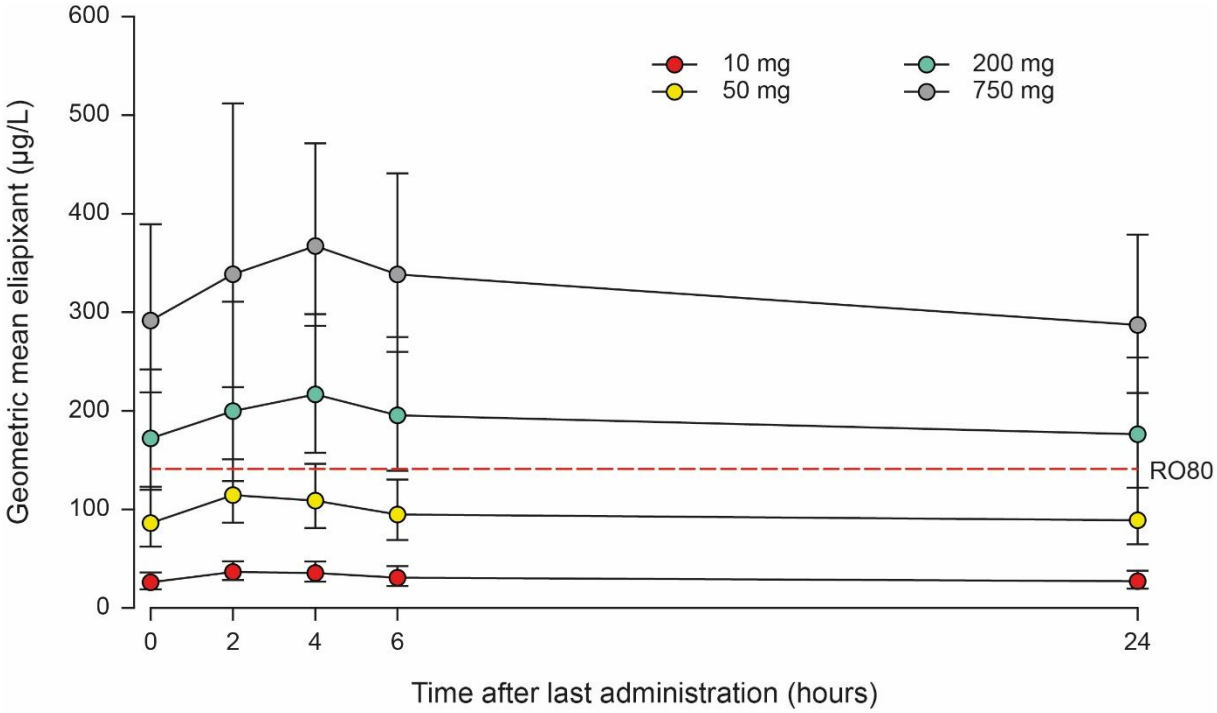
SUPPLEMENTAL FIGURE 1 Geometric mean cough frequencies in periods A and B over 24 hours (a) and awake (b). Figures in parentheses are geometric coefficient of variation.



SUPPLEMENTAL FIGURE 2 Placebo-corrected change in arithmetic mean cough frequency measured over 24 hours and awake, adjusted as for trials of other P2X3 receptor antagonists which appeared to use arithmetic means [28]. Post-hoc descriptive analysis.



SUPPLEMENTAL FIGURE 3 Mean cough severity in periods A and B. Vertical lines indicate SEM. SEM: standard error of the mean; VAS: visual analogue scale.



SUPPLEMENTAL FIGURE 4 Plasma concentrations of eliapixant after multiple dosing (per protocol set). RO80: concentration producing 80% P2X3 receptor occupancy.