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

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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 S1 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-	*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 inhibitors,

stimulating hormone levels >40 mIU mL^{-1}); or

- Woman without childbearing potential 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

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 S2 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 S3 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 S4 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 S5 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 S6 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 S7 Changes in LCQ total score *versus* placebo and baseline

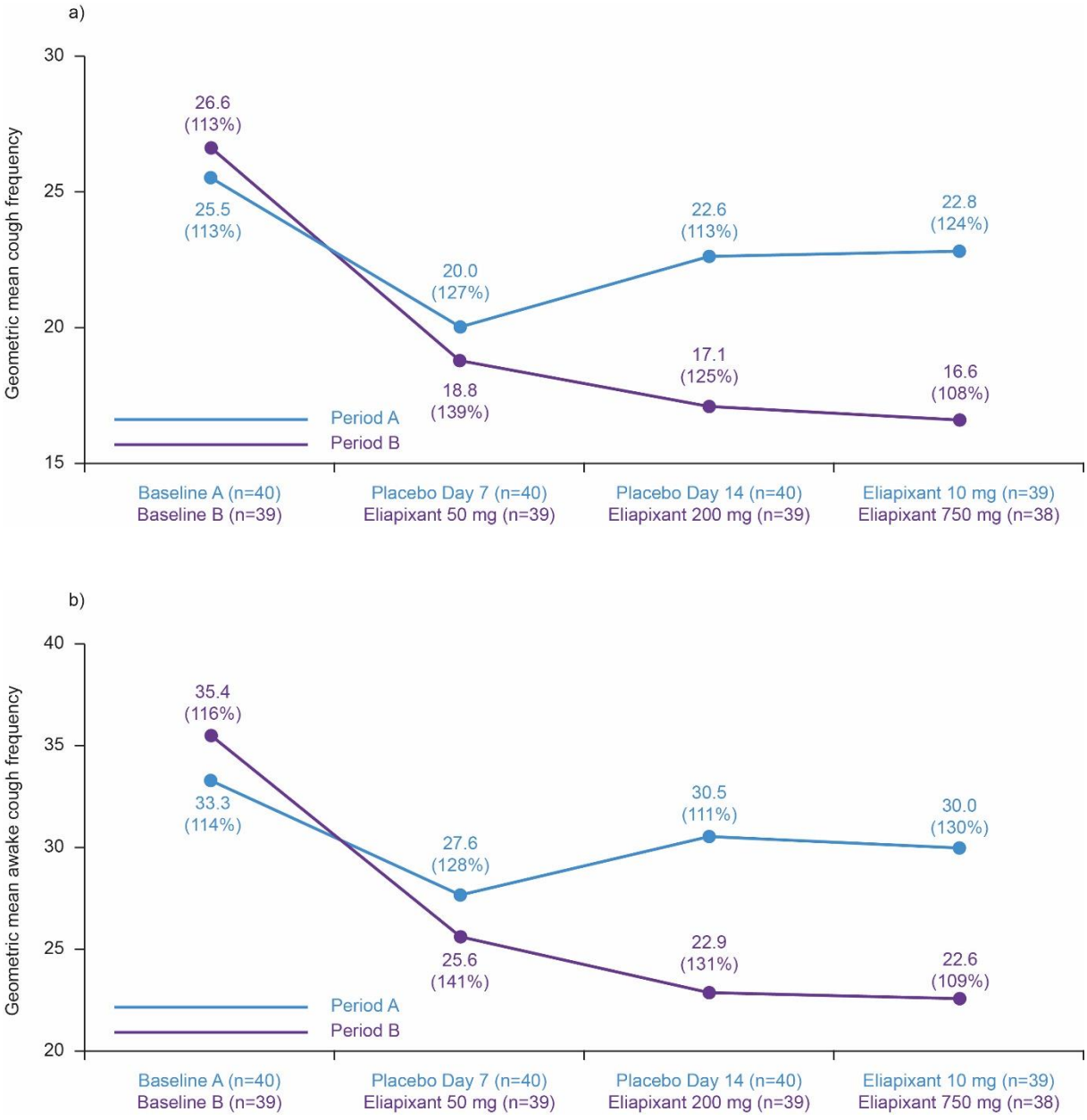
Analysis group	**Change from baseline (90% CL)**	**p-value**	**Change *versus* placebo (90% CL)**	**p-value**
Placebo	0.74 (1.56, −0.08)	NS	– (–, –)	–
Eliapixant 10 mg	0.74 (1.56, −0.07)	NS	0.00 (0.70, −0.71)	NS
Eliapixant 50 mg	1.46 (2.25, 0.62)	<0.05	0.70 (1.43, 0.00)	NS
Eliapixant 200 mg	1.84 (2.64, 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.

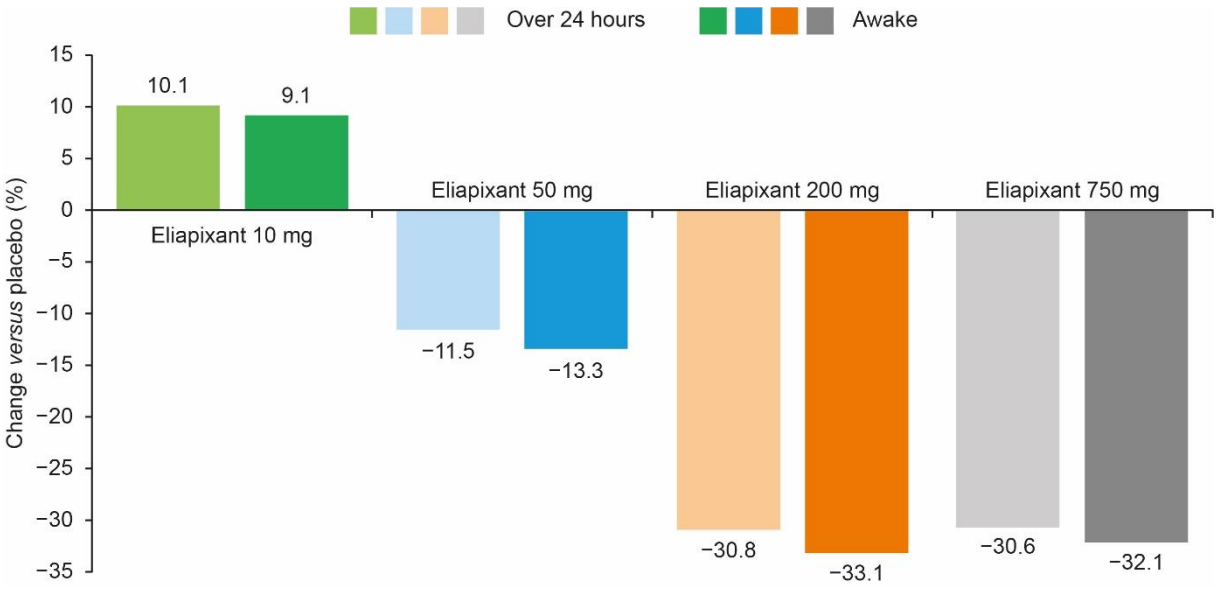
SUPPLEMENTAL TABLE S8 AEs considered by the investigator to be related to study drug

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)

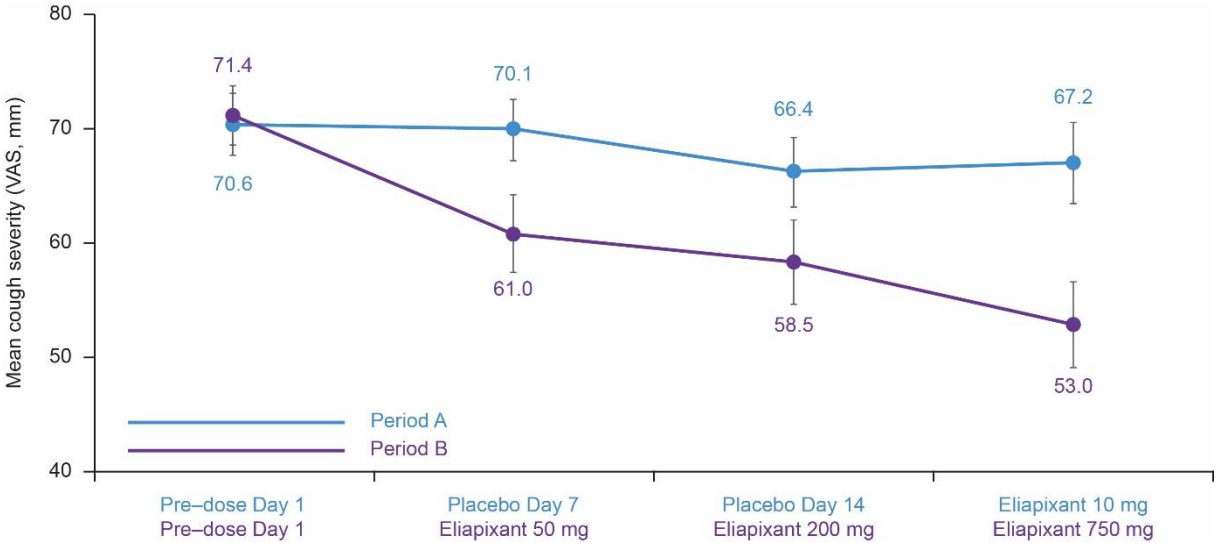
AE: adverse event.



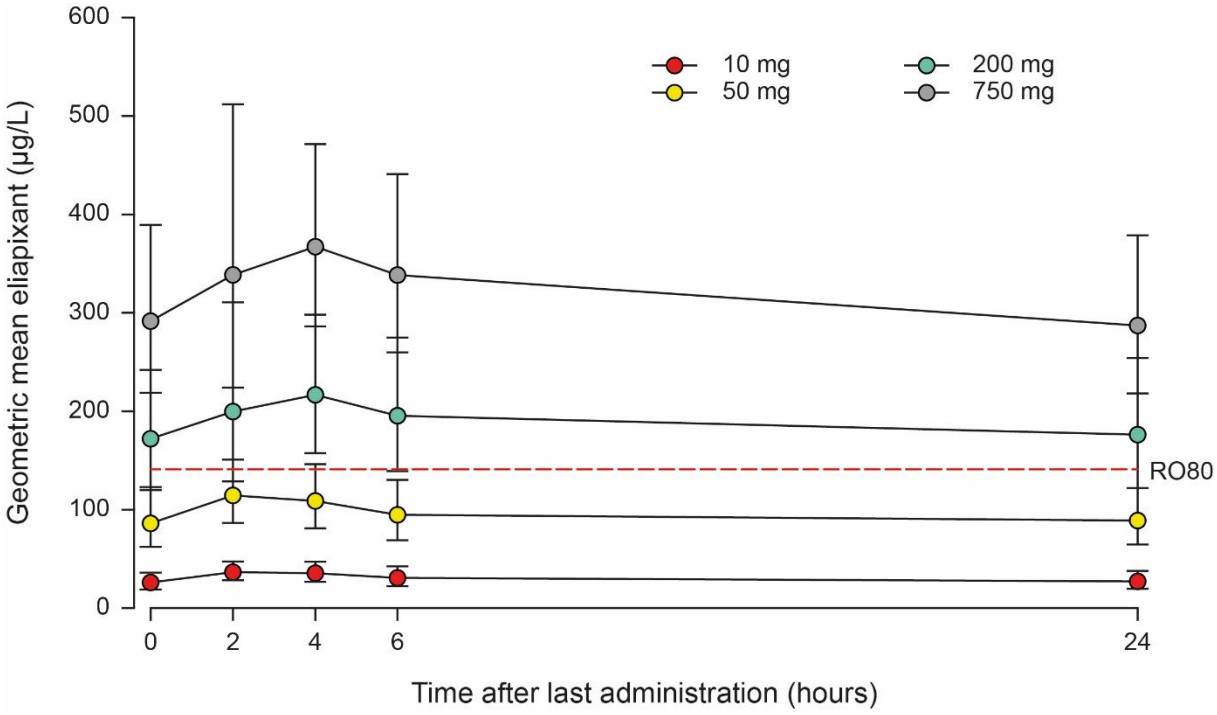
SUPPLEMENTAL FIGURE S1 Geometric mean cough frequencies in periods A and B over 24 hours (a) and awake (b). Figures in parentheses are geometric coefficient of variation.



SUPPLEMENTAL FIGURE S2 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 S3 Mean cough severity in periods A and B. Vertical lines indicate SEM. SEM: standard error of the mean; VAS: visual analogue scale.



SUPPLEMENTAL FIGURE S4 Plasma concentrations of eliapixant after multiple dosing (per protocol set). RO80: concentration producing 80% P2X3 receptor occupancy.