Clinical Pharmacokinetics

Safety, Pharmacodynamics, and Pharmacokinetics of P2X3 Receptor Antagonist Eliapixant (BAY 1817080) in Healthy Subjects: Double-Blind, Randomized Study

Christian Friedrich1 | Klaus Francke1 | Isabella Gashaw1,5 | Christian Scheerans1 | Stefan Klein1 | Lueder Fels1 | Jaclyn A. Smith2 | Thomas Hummel1 | Alyn Morice4

1Bayer AG, Berlin, Germany
2University of Manchester, Manchester University NHS Foundation Trust and Manchester Academic Health Science Centre, Manchester, UK
3Smell and Taste Clinic, Department of Otorhinolaryngology, TU Dresden, Dresden, Germany
4Centre for Clinical Sciences, Hull York Medical School, University of Hull, Hull, UK
5Present address: Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Corresponding author:
Christian Friedrich, Bayer AG, Berlin, Germany

Email: christian.friedrich@bayer.com

SUPPLEMENTAL MATERIAL
Methods

Study design and participants

- Healthy volunteers were recruited from the healthy volunteer database of the contract research organization (Medicines Evaluation Unit, Manchester, UK). In addition they advertised on their website and Facebook that they were looking for healthy volunteers for a new study (without mentioning any further details or specifics of the study).
- The study comprised a 4-week screening period, followed by a 2-week treatment period and a 3-week follow-up.
- Both investigators and subjects were blinded to treatment; tablet formulations for each dose strength of eliapixant or placebo were identical in appearance (size, shape, color) and smell.

Inclusion criteria

Subjects who met all of the following criteria were eligible for inclusion in the study:

1. Signature of the informed consent form before any study-specific tests or procedures were performed.
2. Male; healthy according to complete medical history, including the physical examination, vital signs (blood pressure, heart rate), 12-lead electrocardiogram (ECG), and clinical laboratory tests.
3. Age: 18–45 years (inclusive) at the first screening visit.
4. Body mass index: > 18 kg m\(^{-2}\) and < 30 kg m\(^{2}\).
5. Non-smoker for at least 6 months and with a pack-year history of ≤ 5 years.
6. Subjects who are sexually active and have not been surgically sterilized had to agree to use two reliable and acceptable methods of contraception simultaneously when having sexual intercourse with women of childbearing potential (one method used by the subject 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 a sperm donor for 90 days after dosing. (Acceptable methods of contraception include, for example: (a) condoms [male or female] with or without a spermicidal agent, (b) diaphragm or cervical cap with spermicide, (c) intrauterine device, (d) hormone-based contraception.)
7. Ability to understand and follow study-related instructions.
8. The concentration of the challenge solution inducing at least two coughs at the screening challenge was ≤ 128 mg mL\(^{-1}\) measured at screening by the standardized inhalational cough challenge with the tussive agent adenosine triphosphate (ATP).
Exclusion criteria

Subjects who met any of the following criteria were not eligible for inclusion in the study:

Medical and surgical history

1. Any findings from the medical examination (including medical history, physical examination, vital signs, laboratory tests, and ECG) deviating from normal and deemed by the investigator to be of clinical relevance.
2. Forced expiratory volume in 1 second (FEV$_1$) or forced vital capacity of < 80% of predicted normal at screening.
3. Relevant diseases potentially interfering with the study's aims (e.g., respiratory diseases) within the 4 weeks before screening or between screening and randomization.
4. Any febrile illness within the 4 weeks before screening or between screening and randomization.
5. Any dental appointment within the 2 weeks before screening or between screening and randomization (to exclude, e.g., dental cleaning or any dental procedures that might have had an effect on the study’s aims).
6. Dry mouth (xerostomia).
7. Diseases of the oral mucosa.
8. Medical history of hypogeusia/dysgeusia, or the subject had a dysfunction in his ability to taste, as revealed by the taste-disturbance questionnaire during screening and the pre-dose procedures.
9. Any known presence or history of severe allergies, non-allergic drug reactions, or multiple drug allergies.
10. Known or suspected malignant tumors or carcinoma in situ.
11. Any history of malignant tumors.
12. Any known or suspected benign tumors of the liver and/or pituitary gland.
13. Known liver disease: existing acute or chronic progressive liver disease, e.g., disturbance of bilirubin excretion (Dubin–Johnson and Rotor syndromes); disturbances of bile secretion and flow (cholestasis); presence or history of liver tumors (benign or malignant). (Note: According to this criterion, there must have been an interval of at least 6 months between the subsidence of any viral hepatitis [normalization of liver parameters] and the screening visit.)
14. Any known relevant kidney disease (e.g., glomerulonephritis) or any renal injury associated with multisystem diseases/disorders (e.g., systemic lupus erythematosus, diabetic nephropathy).
15. Known current thyroid disorders requiring treatment.
16. Known metabolic disorders (e.g., diabetes mellitus, severe hypertriglyceridemia).
17. Known cardiovascular disorders requiring treatment.
18. Any history of orthostatic hypotension, fainting spells, and blackouts.
19. Migraine with neurologic symptoms (complicated migraine).
20. Clinically significant depression (current or in the year before screening).
21. Incompletely cured pre-existing diseases for which it can be assumed that the absorption, distribution, metabolism, elimination, and effects of the study drugs will not be normal.
22. Known hypersensitivity to the study medication(s) including components of the preparation.

**Medication, drug use, and special behavioral patterns**

23. Use of opioids (including codeine) during the week before screening.
24. Use of any over-the-counter cough mixture within the 24 hours before screening.
25. Regular use of therapeutic or recreational drugs, e.g., carnitine products, anabolics, high-dose vitamins.
26. A history of alcohol or drug abuse within the last 2 years.
27. Intake of drugs with a long half-life (≥ 24 hours) within a time frame of < 5 half-lives before study drug administration.
28. Use of any systemic or topically active drug(s) that might have influenced the results of the trial within the 14 days before study drug administration or during the trial until follow-up. (Note: This includes drugs that might have affected the pharmacokinetics of eliapixant, e.g., laxatives, loperamide, metoclopramide, antacids, H₂-receptor antagonists, CYP3A4 inducers, strong CYP3A4 inhibitors.)
29. Regular daily consumption of more than 500 mL of usual-strength beer or the equivalent quantity of approximately 3 units of alcohol in another form.
30. Donation of blood or plasmapheresis within the month before screening and before randomization, and from randomization until the follow-up visit.
31. Inability to taste at least the second highest concentration of each taste quality using the taste strips at screening.
**ECG, blood pressure, heart rate**

32. Clinically relevant ECG findings, such as a second- or third-degree atrioventricular block, prolongation of the QRS complex over 120 ms at screening or pre-dose on Day –0.

33. Corrected QT intervals according to Bazett’s formula over 450 ms (mean of triplicate measurements, ECG recordings after at least 10 minutes of supine rest) at screening or pre-dose on Day –0.

34. Systolic blood pressure below 100 mmHg or above 145 mmHg (after at least 10 minutes of supine rest) at screening or pre-dose on Day –0.

35. Diastolic blood pressure below 60 mmHg or above 90 mmHg (after at least 10 minutes of supine rest) at screening or pre-dose on Day –0.

36. Heart rate below 50 beats min⁻¹ or above 95 beats min⁻¹ (after at least 10 minutes of supine rest) at screening or pre-dose on Day –0.

**Physical examination**

37. Clinically relevant findings in the physical examination.

**Neurologic examination**

38. Clinically relevant findings in the orientating, basic neurologic examination.

**Laboratory examination**

39. Clinically relevant deviations of the screening laboratory parameters from their respective reference ranges (especially alanine transaminase, aspartate transaminase, bilirubin > upper limit of normal).

40. Positive results for hepatitis B virus surface antigen, hepatitis C virus antibodies, or human immune deficiency virus antibodies (anti-HIV 1 + 2).

41. Positive result in urine drug screening, or positive alcohol breath test, or positive urine cotinine test.

**Other**

42. Participation in another trial and received an investigational drug within the 2 months, or a longer and more appropriate time as determined by the investigator (e.g., approximately 5 half-lives of the previous investigational drug), before first study drug administration.

43. Subject was in custody by order of an authority or a court of law.
44. Criteria that in the opinion of the investigator precluded participation for scientific reasons, for reasons of compliance, or for reasons of the subject’s safety.

45. Previous assignment to treatment (i.e., randomization) during this study.

46. Scheduled (elective) surgery or planned hospitalization during the period between signing the informed consent form and 6 weeks after the last administration of the study drug.

47. Prolonged immobilization, major surgery, any surgery to the legs, or major trauma, unless complete remobilization was achieved at least 4 weeks before the first screening examination.

48. Close affiliation with the investigation site, e.g., a close relative of the investigator or a dependent person (e.g., employee or student of the investigation site).

49. Subject was an employee of the sponsor/study site.

50. Inability/unwillingness to comply with study restrictions.

Pharmacokinetic model simulations for selection of doses

Based on single-dose data from the first-in-humans (FiH) study (unpublished data, Bayer AG, Berlin, Germany), a population pharmacokinetic (popPK) analysis for eliapixant was conducted via non-linear mixed-effects modeling using NONMEM (ICON Development Solutions, version 7.3). The pharmacokinetic data of all dose steps from the FiH study with and without food (continental breakfast/American breakfast) were adequately described with a two-compartment popPK model with linear disposition kinetics and a dose- and food (type)-dependent effect on the relative bioavailability. The popPK analysis for eliapixant was conducted via non-linear mixed-effects modeling using NONMEM. The popPK model parameterized for continental breakfast was used for in silico simulations to select the final four different three-times-daily loading and twice-daily maintenance dose scenarios for the multiple-dose exposure study to achieve the targeted trough drug concentrations in plasma per dose step quickly, as mentioned in the main text.

Investigation of dose proportionality

To investigate dose proportionality, an explorative analysis of variance (including treatment as single factor) was performed on the log-transformed pharmacokinetic parameters $\text{AUC}(0–12)$, $\text{md/D}$ and $\text{C}_{\text{max,md}}$, $\text{D}$. Based on these analyses, point estimates and 90% confidence intervals (CIs) of the treatment effect of each dose were calculated and then re-transformed to the original scale. A confirmatory statistical analysis was not intended.

In addition, the so-called power model was applied in order to assess dose proportionality. Here, the following model is assumed (using AUC as an example):
\( AUC = c \times \exp(\beta \times \log \text{dose}) \times \exp(\epsilon) \). For logarithmized pharmacokinetic parameters, this reduces to a linear regression model:

\[
\log AUC = c + \beta \times \log \text{dose} + \epsilon
\]

Point estimates of slope as well as 90% CI of slope parameter were used to characterize the amount of dose proportionality. Dose proportionality may be declared over the dose range used when the CI for the slope \( \beta \) is contained within \((\beta_L, \beta_U)\), where

\[
\beta_L = 1 + \ln(0.8)/\ln(\text{max [dose]}/\text{min [dose]}) \quad \text{and} \quad \beta_U = 1 + \ln(1.25)/\ln(\text{max [dose]}/\text{min [dose]}).
\]

For AUC/D, C\(_{\text{max}}\)/D, AUC\(_{\text{md}}\)/D, and C\(_{\text{max,md}}\)/D of all analytes, box-plots were produced.

AUC(0–12)/D, area under the concentration–time curve from zero to infinity divided by dose; AUC\(_{\text{md}}\)/D; area under the concentration–time curve from zero to infinity after multiple dosing divided by dose; C\(_{\text{max}}\)/D, maximum observed drug concentration in measured matrix at steady state during a dosage interval divided by dose; C\(_{\text{max,md}}\)/D, maximum observed drug concentration in measured matrix after multiple dose administration during a dosage interval, taken directly from analytical data divided by dose.

As part of the demographic assessment, body weight was measured with the subject in light indoor clothing and without shoes, using an electronic scale with a digital display with measurement units of 0.1 kg. The dose of eliapixant or placebo was not adjusted for body weight.

**ATP cough challenge test**

The ATP cough challenge test was performed at the study site by trained personnel according to the study reference manual. ATP challenge solutions were prepared using ATP in sterile 0.9% sodium chloride solution.

ATP solutions at concentrations of 0.125–128 mg mL\(^{-1}\) were used at screening. For the ATP challenge at day \(-1\) and day 13, solutions may have included concentrations of up to 512 mg mL\(^{-1}\) of ATP. Subjects inhaled doubling concentrations of ATP while cough frequency was monitored with the VitaloJAK cough recorder until the subject’s maximum tolerated dose was achieved.

The subjects were instructed to inhale the ATP slowly through a calibrated nebulizer attached to a dosimeter and to “cough as much as they feel they need to.” The number of coughs within 15 seconds of inhaling ATP was recorded. Each concentration of ATP was inhaled four times, 30 seconds apart, with the cough frequency being calculated as the cumulative number of coughs for all four inhalations. FEV\(_1\) was monitored before and after the challenge to assess for signs of bronchoconstriction.
The challenge was discontinued if the subject experienced severe side effects or showed a clear wish to stop; the highest dose administered was recorded as the subject’s maximum tolerated dose.

After the cough challenge session, the results from the cough recorder were processed to determine C2 and C5 (the concentration levels of tussive agent that induce at least two or five coughs, respectively, within 15 seconds after ATP inhalation). The maximally effective dose and the dose eliciting half-maximum response were also determined.

C2 and C5 levels were analyzed using frequency tables by treatment, time point, and inhalation number.

Taste assessments

To evaluate potential effects of eliapixant on perception of taste sensation, quantitative and subjective taste evaluation before and following drug administration was conducted. The following methods to assess taste perception were used:

- Taste strips
- Dysgeusia questionnaire
- Adverse event reporting.

Taste strips

The taste strips (Burghart Messtechnik GmbH) are a validated test method for ascertaining tasting performance (International Organization for Standardization certified). The following concentrations are applied on the taste strips:

- Sweet: 0.4, 0.2, 0.1, 0.05 g mL\(^{-1}\) sucrose
- Sour: 0.3, 0.165, 0.09, 0.05 g mL\(^{-1}\) citric acid
- Salty: 0.25, 0.1, 0.04, 0.016 g mL\(^{-1}\) sodium chloride
- Bitter: 0.006, 0.0024, 0.0009, 0.0004 g mL\(^{-1}\) quinine hydrochloride.

The taste strips are used to check the tasting performance of the whole mouth by placing a taste strip on the tongue and closing the mouth (the subject can move the tongue).

At screening, the subject received four taste strips, each soaked with the second highest concentration of one of the four compounds, and a control strip, to experience the quality of sweet, sour, salt, bitter, and the paper itself. Afterwards and between the four taste strips, the mouth was rinsed, if the subject wanted to, with a sip of tap water.
During treatment, the taste strips were presented in a randomized order (increasing concentration for each quality) and placed on the tongue. The subjects’ task was to choose one of five possible answers on a form (sweet, sour, salty, bitter, no taste). Before and after each testing, the mouth was rinsed with a sip of tap water according to individual needs.

To maximize blinding of the test subjects with respect to the taste strip assessment in this study, three different sequences of the taste strips were produced. Subsequently, these three sequences were called A, B, and C.

Taste was measured on three occasions: once in pretreatment and twice in treatment. Therefore, it was randomly determined which sequence a subject received at a certain time point. All subjects started with sequence A during pretreatment. Under treatment, subjects were given either strip sequence B at the first occasion and C at the second occasion, or vice versa. Thus, subjects were randomized to group ABC or ACB. This randomization list was produced by the randomization management department. The suffix “TS” was used in the study identifier section of the Randomization Request Form to clarify that this Randomization Request Form is for the randomization of the three taste strip sequences only.

For the generation of the three test strip sequences, Statistical Analysis Software (SAS) 9.4 was used, to be run at a local server. The output of this program was a PDF document containing a list of the three test strip sequences and an SAS file with the same content.

The PDF and SAS files were stored by the randomization department at Bayer until the blind was broken. The randomization department in turn sent the PDF file to the responsible person at the investigational site, together with a respective note to file. Technically, the PDF file is an appendix to the note to file. The investigational site used the PDF file to apply the taste strips according to the test strip sequences (A, B, or C).

The SAS file was sent to the Bayer Data Management programming department by the randomization department, together with the randomization list for the taste strips.

During the test, the lowest concentration that could be identified by the respective subject was determined for each taste quality at baseline and after treatment.

For the sake of explanation, the lowest concentration of each taste quality was expected to be identified by half of the healthy subjects only, and the highest concentration by approximately 100% of the subjects.

Dysgeusia (by questionnaire for taste disturbance)

Dysgeusia is an umbrella term for taste dysfunction that includes: hypogeusia, a quantitative decrease in taste sensation; parageusia, a distorted taste sensation in the presence of a taste stimulus; and phantogeusia, a taste
sensation in the absence of a taste stimulus. A questionnaire that contains corresponding questions was used to identify subjects affected by dysgeusia and to describe the quality of dysgeusia.

**Randomization and blinding**

At the beginning of the first treatment period (i.e., day 0 after final check of inclusion and exclusion criteria), subjects who met the entry criteria were sequentially assigned to a unique randomization number in ascending order. Each randomization number was assigned randomly to one of the treatments (active treatment or placebo) according to a computer-generated randomization list provided by Data Sciences and Analytics.

The study used block randomization. The randomization list was determined by a validated SAS program, and sent from the Bayer randomization department to the packaging department. There were no other recipients before intervention was assigned. Thus the whole study team was blinded. Participants received the medication, which was prepared in advance for their randomization number by the packaging department. The random allocation sequence was generated by Bayer’s randomization department, not being involved with the study except for randomization/unblinding procedures. Participants were enrolled by the investigator of the study center (Jaclyn Smith). Participants received the lowest randomization number still available on the day of first treatment, which was linked by randomization list to active/placebo treatment.

The study was performed according to a double-blind design, with investigators and subjects blinded to treatment assignment (i.e., eliapixant or placebo). Tablet formulations for each dose strength of active product and placebo were identical in appearance (i.e., size, shape, color) and smell. The study data remained blinded until database lock and authorization of data release according to standard operating procedures.

**Statistical analysis**

No formal statistical sample size estimation was performed for this study. No formal statistical interim analyses were performed. The following analysis sets were used in the safety or efficacy analyses:

- The safety analysis set comprised all subjects who received at least one dose of the study medication.
- The pharmacokinetic analysis set comprised subjects who received at least one dose of eliapixant and had valid pharmacokinetic profiles.
- The per-protocol analysis set included all subjects who completed the study without validity findings. This analysis set was used for the taste score assessments.
• The modified per-protocol analysis set included subjects who completed the study without validity findings affecting the analysis of taste scores or pharmacodynamics; this analysis set was used for the ATP cough challenge test.

**Stopping criteria**

The protocol stipulated that the subsequent dose level would not be started if one of the following criteria were met:

• Occurrence of serious adverse events (SAEs) assessed as being related to eliapixant in one or more subjects.

• Occurrence of severe adverse events (AEs) assessed as being related to eliapixant in more than two subjects at the same dose level. Additionally, a thorough assessment of severe AEs related to eliapixant at different dose levels as well as the accumulation of moderate AEs related to eliapixant was made.

• Clinically relevant safety laboratory deviation (confirmed by analysis of two blood samples; additional laboratory tests may be necessary) assessed as being related to eliapixant in more than two subjects of the same dose level receiving eliapixant.
Table S1 Baseline demographics and characteristics of subjects (per-protocol set)

|                     | Eliapixant | Placebo | Total |
|---------------------|------------|---------|-------|
|                     | 10 mg      | 50 mg   | 200 mg| 750 mg|
|                     | n = 9      | n = 9   | n = 8 | n = 8 |
| Sex, n (%)          |            |         |       |       |
| Male                | 9 (100)    | 9 (100) | 8 (100)| 8 (100)| 11 (100)| 45 (100) |
| Race, n (%)         |            |         |       |       |         |         |
| Asian               | 0          | 1 (11)  | 1 (13)| 0     | 0       | 2 (4)   |
| Black/African American | 2 (22)   | 0       | 0     | 1 (13)| 2 (18)  | 5 (11)  |
| White               | 7 (78)     | 8 (89)  | 7 (88)| 7 (88)| 9 (82)  | 38 (84) |
| Age (years)         |            |         |       |       |         |         |
| Mean (SD)           | 31.0 (7.0) | 30.0 (7.0)| 29.9| 30.9 (7.4)| 30.9 (7.4)| 29.6 (7.6)| 30.2 (7.0) |
| Range               | 19–43      | 22–38   | 22–39| 20–41 | 19–43   | 19–43   |
| BMI (kg m⁻²)        |            |         |       |       |         |         |
| Mean (SD)           | 26.4 (2.5) | 25.5 (2.9)| 26.0| 24.8 (2.3)| 25.4 (2.3)| 25.6 (2.6) |
| Smoking history, n (%)|          |         |       |       |         |         |
| Never               | 8 (89)     | 9 (100) | 7 (88)| 7 (88)| 9 (82)  | 40 (89) |
| Former              | 1 (11)     | 0       | 1 (13)| 1 (13)| 2 (18)  | 5 (11)  |

Percentages may not add to 100% due to rounding

*BMI* body mass index, *SD* standard deviation
### Table S2 Baseline demographics and characteristics of subjects (modified per-protocol set)

|                      | Eliapixant |           |           |           | Placebo | Total |
|----------------------|------------|-----------|-----------|-----------|---------|-------|
|                      | 10 mg      | 50 mg     | 200 mg    | 750 mg    | n = 10  | n = 40 |
|                      | n = 7      | n = 8     | n = 7     | n = 8     |         |       |
| Sex, n (%)           |            |           |           |           |         |       |
| Male                 | 7 (100)    | 8 (100)   | 7 (100)   | 8 (100)   | 10 (100)| 40 (100)|
| Race, n (%)          |            |           |           |           |         |       |
| Asian                | 0          | 1 (13)    | 1 (14)    | 0         | 0       | 2 (5) |
| Black/African American| 1 (14)    | 0         | 0         | 1 (13)    | 2 (20)  | 4 (10) |
| White                | 6 (86)     | 7 (88)    | 6 (86)    | 7 (88)    | 8 (80)  | 34 (85)|
| Age (years)          |            |           |           |           |         |       |
| Mean (SD)            | 29.6 (6.2) | 29.3 (7.1)| 29.0 (7.5)| 30.9 (7.4)| 28.6 (7.1)| 29.4 (6.8)|
| Range                | 19–35      | 22–38     | 22–39     | 20–41     | 19–43   | 19–43 |
| BMI (kg m²)          |            |           |           |           |         |       |
| Mean (SD)            | 26.3 (2.9) | 25.1 (2.9)| 25.7 (3.3)| 24.8 (2.3)| 25.2 (2.3)| 25.4 (2.6)|
| Smoking history, n (%)|          |           |           |           |         |       |
| Never                | 6 (86)     | 8 (100)   | 7 (100)   | 7 (88)    | 8 (80)  | 36 (90)|
| Former               | 1 (14)     | 0         | 0         | 1 (13)    | 2 (20)  | 4 (10)|

Percentages may not add to 100% due to rounding

*BMI* body mass index, *SD* standard deviation
|                    | Eliapixant                                      | Total | n = 34 |
|--------------------|-------------------------------------------------|-------|--------|
|                    | 10 mg n = 9                                     | 50 mg n = 9 | 200 mg n = 8 | 750 mg n = 8 |
| Sex, n (%)         |                                                 |       |        |
| Male               | 9 (100)                                         | 9 (100)| 8 (100)| 8 (100)   | 34 (100)    |
| Race, n (%)        |                                                 |       |        |
| Asian              | 0                                               | 1 (11)| 1 (13)| 0         | 2 (6)       |
| Black/African American | 2 (22)                                        | 0     | 0     | 1 (13)    | 3 (9)       |
| White              | 7 (78)                                          | 8 (89)| 7 (88)| 7 (88)    | 29 (85)     |
| Age (years)        |                                                 |       |        |
| Mean (SD)          | 31.0 (7.0)                                      | 30.0 (7.0)| 29.9 (7.4)| 30.9 (7.4)| 30.4 (6.9) |
| Range              | 19–43                                           | 22–38 | 22–39 | 20–41     | 19–43       |
| BMI (kg m\(^{-2}\))|                                                 |       |        |
| Mean (SD)          | 26.4 (2.5)                                      | 25.5 (2.9)| 26.0 (3.1)| 24.8 (2.3)| 25.7 (2.7) |
| Smoking history, n (%) |                                             |       |        |
| Never              | 8 (89)                                          | 9 (100)| 7 (88)| 7 (88)    | 31 (91)     |
| Former             | 1 (11)                                          | 0     | 1 (13)| 1 (13)    | 3 (9)       |

Percentages may not add to 100% due to rounding

*BMI* body mass index, *SD* standard deviation
Table S4 Baseline values and changes from baseline for overall taste scores from taste strips (per-protocol set)

| Time point | Change from baseline | n | Mean (SD) | n | Mean (SD) |
|------------|----------------------|---|-----------|---|-----------|
| Eliapixant 10 mg | Baseline | 9 | 10.4 (2.9) | 9 | – 1.0 (1.9) |
| | Day 3 | 9 | 9.4 (3.4) | 9 | – 1.0 (1.9) |
| | Day 13 | 9 | 10.0 (3.6) | 9 | – 0.4 (2.4) |
| Eliapixant 50 mg | Baseline | 9 | 11.0 (2.5) | 9 | 0.4 (1.8) |
| | Day 3 | 9 | 11.4 (2.4) | 9 | 0.4 (1.8) |
| | Day 13 | 8 | 11.4 (3.6) | 8 | 0.3 (2.4) |
| Eliapixant 200 mg | Baseline | 8 | 13.0 (1.1) | 8 | – 0.9 (2.1) |
| | Day 3 | 8 | 12.1 (1.9) | 8 | – 0.9 (2.1) |
| | Day 13 | 7 | 12.1 (2.0) | 7 | – 0.9 (2.1) |
| Eliapixant 750 mg | Baseline | 8 | 13.1 (1.6) | 8 | – 1.5 (1.9) |
| | Day 3 | 8 | 11.6 (2.9) | 8 | – 1.5 (1.9) |
| | Day 13 | 8 | 11.5 (2.7) | 8 | – 1.6 (1.9) |
| Placebo | Baseline | 11 | 12.2 (2.6) | 11 | – 0.8 (1.5) |
| | Day 3 | 11 | 11.8 (2.3) | 11 | – 0.8 (1.5) |
| | Day 13 | 11 | 11.0 (2.0) | 11 | – 0.3 (2.4) |

Baseline: last measurement before treatment

SD standard deviation
Table S5 Baseline values and changes from baseline for individual taste scores from taste strips (per-protocol set): a) sweet, b) sour, c) salty, d) bitter

|                  | Time point | Change from baseline |
|------------------|------------|----------------------|
|                  |            | n | Mean (SD) | n | Mean (SD) |
| **Eliapixant 10 mg** | Baseline  | 9 | 3.2 (0.7) | 9 | – 1.1 (0.8) |
|                  | Day 3      | 9 | 2.1 (0.9) | 9 | – 0.3 (0.9) |
| **Eliapixant 50 mg** | Baseline  | 9 | 3.0 (0.9) | 9 | 0.0 (0.7) |
|                  | Day 3      | 9 | 3.0 (0.7) | 9 | 0.0 (0.7) |
| **Eliapixant 200 mg** | Baseline  | 8 | 3.8 (0.5) | 8 | – 0.5 (0.8) |
|                  | Day 3<sup>a</sup>  | 8 | 3.3 (0.7) | 8 | – 0.6 (0.8) |
|                  | Day 13<sup>b</sup> | 7 | 3.1 (0.9) | 7 | 0.0 (0.9) |
| **Eliapixant 750 mg** | Baseline  | 8 | 3.1 (0.8) | 8 | 0.1 (0.6) |
|                  | Day 3<sup>a</sup>  | 8 | 3.3 (0.7) | 8 | 0.0 (0.9) |
|                  | Day 13<sup>b</sup> | 8 | 3.1 (0.8) | 8 | 0.0 (0.9) |
| **Placebo**      | Baseline  | 11 | 3.5 (0.5) | 6 | – 0.3 (0.5) |
|                  | Day 3      | 6 | 3.2 (0.4) | 6 | – 0.5 (0.5) |
|                  | Day 13     | 6 | 3.0 (0.6) | 6 | – 0.5 (0.5) |

Baseline: last measurement before treatment
SD standard deviation
<sup>a</sup>Assessment at Day 2, 23 hours, 30 minutes
<sup>b</sup>Assessment at Day 12, 23 hours, 30 minutes
### b) Time point Change from baseline

| Treatment      | Time Point | n | Mean (SD) | n  | Mean (SD) |
|----------------|------------|---|-----------|---|-----------|
| Eliapixant 10 mg | Baseline  | 9 | 1.8 (1.0) |   |           |
|                | Day 3      | 9 | 2.2 (0.4) | 9 | 0.4 (1.0) |
|                | Day 13     | 9 | 2.3 (0.5) | 9 | 0.6 (1.2) |
| Eliapixant 50 mg | Baseline  | 9 | 2.7 (0.5) |   |           |
|                | Day 3      | 9 | 2.3 (0.7) | 9 | –0.3 (0.7) |
|                | Day 13     | 9 | 2.2 (0.7) | 9 | –0.4 (0.7) |
| Eliapixant 200 mg | Baseline | 8 | 2.6 (0.7) |   |           |
|                | Day 3^a    | 8 | 2.5 (0.5) | 8 | –0.1 (0.6) |
|                | Day 13^b   | 7 | 2.1 (0.7) | 7 | –0.6 (1.0) |
| Eliapixant 750 mg | Baseline | 8 | 2.6 (0.5) |   |           |
|                | Day 3^a    | 8 | 2.6 (0.5) | 8 | 0.0 (0.9) |
|                | Day 13^b   | 8 | 2.1 (0.6) | 8 | –0.5 (0.5) |
| Placebo        | Baseline  | 11| 2.5 (0.9) |   |           |
|                | Day 3      | 6 | 2.7 (0.5) | 6 | 0.3 (0.8) |
|                | Day 13     | 6 | 2.3 (0.8) | 6 | 0.0 (1.5) |

Baseline: last measurement before treatment
SD standard deviation
^aAssessment at Day 2, 23 hours, 30 minutes
^bAssessment at Day 12, 23 hours, 30 minutes
|                        | Time point | Change from baseline |
|------------------------|------------|----------------------|
|                        | n  | Mean (SD)  | n | Mean (SD) |
| **Eliapixant 10 mg**   |    |            |   |           |
| Baseline               |  9 | 2.9 (1.1)  |  9 | – 0.2 (1.2) |
| Day 3                  |  9 | 2.7 (1.2)  |  9 |             |
| Day 13                 |  9 | 2.6 (1.1)  |  9 | – 0.3 (0.9) |
| **Eliapixant 50 mg**   |    |            |   |           |
| Baseline               |  9 | 2.3 (1.0)  |  9 |             |
| Day 3                  |  9 | 2.9 (1.1)  |  9 | 0.6 (0.7)   |
| Day 13                 |  9 | 2.2 (1.6)  |  9 | – 0.1 (1.3) |
| **Eliapixant 200 mg**  |    |            |   |           |
| Baseline               |  8 | 3.4 (0.5)  |  8 |             |
| Day 3<sup>a</sup>      |  8 | 3.0 (0.8)  |  8 | – 0.4 (0.7) |
| Day 13<sup>b</sup>     |  7 | 3.4 (0.8)  |  7 | 0.0 (1.0)   |
| **Eliapixant 750 mg**  |    |            |   |           |
| Baseline               |  8 | 3.8 (0.5)  |  8 |             |
| Day 3<sup>a</sup>      |  8 | 2.8 (0.7)  |  8 | – 1.0 (0.5) |
| Day 13<sup>b</sup>     |  8 | 3.0 (1.4)  |  8 | – 0.8 (1.0) |
| **Placebo**            |    |            |   |           |
| Baseline               | 11 | 3.3 (0.8)  | 11 |             |
| Day 3                  |  6 | 3.0 (0.9)  |  6 | – 0.3 (0.8) |
| Day 13                 |  6 | 3.5 (0.8)  |  6 | 0.2 (1.0)   |

Baseline: last measurement before treatment
SD standard deviation
<sup>a</sup>Assessment at Day 2, 23 hours, 30 minutes
<sup>b</sup>Assessment at Day 12, 23 hours, 30 minutes
|                     | Time point | Change from baseline |
|---------------------|------------|----------------------|
|                     | n          | Mean (SD)            | n          | Mean (SD)            |
| Eliapixant 10 mg    | Baseline   | 9 2.6 (1.4)          | 9          | – 0.1 (1.1)          |
|                     | Day 3      | 9 2.4 (1.5)          | 9          | – 0.3 (1.5)          |
|                     | Day 13     | 9 2.2 (1.6)          | 9          | – 0.3 (1.5)          |
| Eliapixant 50 mg    | Baseline   | 9 3.0 (1.1)          | 9          | 0.2 (1.2)            |
|                     | Day 3      | 9 3.2 (0.8)          | 9          | 0.2 (1.2)            |
|                     | Day 13     | 8 3.4 (1.4)          | 8          | 0.3 (0.7)            |
| Eliapixant 200 mg   | Baseline   | 8 3.3 (0.9)          | 8          | 0.1 (1.0)            |
|                     | Day 3<sup>a</sup> | 8 3.4 (0.7) | 8          | 0.1 (1.0)            |
|                     | Day 13<sup>b</sup> | 7 3.4 (0.5) | 7          | 0.3 (1.1)            |
| Eliapixant 750 mg   | Baseline   | 8 3.6 (0.7)          | 8          | – 0.6 (0.7)          |
|                     | Day 3<sup>a</sup> | 8 3.0 (1.4) | 8          | – 0.6 (0.7)          |
|                     | Day 13<sup>b</sup> | 8 3.3 (1.2) | 8          | – 0.4 (0.7)          |
| Placebo             | Baseline   | 11 2.9 (1.3)         | 6          | – 0.5 (1.0)          |
|                     | Day 3      | 6 2.2 (1.5)          | 6          | 0.3 (1.5)            |
|                     | Day 13     | 6 3.0 (1.1)          | 6          | 0.3 (1.5)            |

Baseline: last measurement before treatment

<sup>SD</sup> standard deviation

<sup>a</sup>Assessment at Day 2, 23 hours, 30 minutes

<sup>b</sup>Assessment at Day 12, 23 hours, 30 minutes
Table S6 ATP cough challenge test results (modified per-protocol analysis set)

|               | Eliapixant | Placebo  |
|---------------|------------|----------|
|               | 10 mg      | 50 mg    | 200 mg   | 750 mg   | \( n = 10 \) |
|               | \( n = 7 \) | \( n = 8^a \) | \( n = 7^b \) | \( n = 8 \) |

Before treatment

| Lowest [ATP] (mg mL\(^{-1}\)) | C2 | C5       | C2 | C5       | C2 | C5       | C2 | C5       |
|-------------------------------|----|----------|----|----------|----|----------|----|----------|
|                               | 4  | 8        | 8  | 8        | 8  | 0.5      |
| Subjects with C2 at highest   | 6 (86) | 7 (100) | 5 (71) | 4 (50) | 8 (80) |
| [ATP],\(^c\) \( n (\%) \)    | 2 (29) | 3 (43) | 2 (29) | 0      | 2 (20) |
| Subjects with C5 at highest   | 15 (5–38) | 19 (8–23) | 10 (2–44) | 8 (0–16) | 13 (0–34) |
| Median (range) cough counts at highest [ATP]\(^c\) | 18 (6–36) | 14 (4–28) | 13 (3–35) | 9 (0–23) | 11 (0–28) |

After treatment

| Lowest [ATP] (mg mL\(^{-1}\)) | C2 | C5       | C2 | C5       | C2 | C5       | C2 | C5       |
|-------------------------------|----|----------|----|----------|----|----------|----|----------|
|                               | 16 | 16       | 0.25 | 32       | 2  |          |
| Subjects with C2 at highest   | 6 (86) | 7 (88) | 4 (67) | 6 (75) | 6 (60) |
| [ATP],\(^c\) \( n (\%) \)    | 2 (29) | 1 (13) | 1 (17) | 1 (13) | 2 (20) |
| Subjects with C5 at highest   | 18 (6–36) | 14 (4–28) | 13 (3–35) | 9 (0–23) | 11 (0–28) |
| Median (range) cough counts at highest [ATP]\(^c\) | 18 (6–36) | 14 (4–28) | 13 (3–35) | 9 (0–23) | 11 (0–28) |

Data are shown for all four inhalations of each concentration combined

\([ATP]\) ATP concentration, C2/5 ≥ 2/5 coughs observed

\(^a\) \( n = 7 \) before treatment

\(^b\) \( n = 6 \) after treatment

\(^c\) 512 mg mL\(^{-1}\)
Fig. S1 Geometric mean (SD) plasma concentrations of eliapixant after the final dose (semi-logarithmic scale). $h$ hours, LLOQ lower limit of quantification (1 μg L$^{-1}$), SD standard deviation