




First-in-human study of eliapixant (BAY 1817080), a highly selective P2X3 receptor antagonist: Tolerability, safety and pharmacokinetics

Stefan Klein¹ | Isabella Gashaw¹  | Sybille Baumann² | Xinying Chang¹ |
Thomas Hummel³  | Uwe Thuß⁴ | Christian Friedrich¹ 

¹Bayer AG, Berlin, Germany

²CRS Clinical Research Services Berlin GmbH, Berlin, Germany

³Department of Otorhinolaryngology, TU Dresden, Dresden, Germany

⁴Bayer AG, Wuppertal, Germany

Correspondence

Christian Friedrich, Research & Development, Pharmaceuticals, Experimental Medicine GT/CMR, Bayer AG, 13342, Berlin, Germany.
Email: christian.friedrich@bayer.com

Aims: Neuronal hypersensitisation due to adenosine triphosphate-dependent P2X3 receptor signalling plays a significant role in several disorders including chronic cough and endometriosis. This first-in-human study of eliapixant (BAY 1817080) investigated the tolerability, safety and pharmacokinetics (PK) of single doses of eliapixant, including the effect of food and coadministration with a CYP3A inhibitor on eliapixant relative bioavailability.

Methods: In this randomised, double-blind phase I study (NCT02817100), 88 healthy male subjects received single ascending doses of immediate-release eliapixant (10–800 mg) tablets or placebo under fasted conditions, with food (low-fat continental or high-fat American breakfast) or with itraconazole (fasted state). PK parameters, dose proportionality, adverse events and taste assessments (taste strips; dysgeusia questionnaire) were evaluated.

Results: Eliapixant had a long half-life (23.5–58.9 h [fasted state]; 32.8–43.8 h [high-fat breakfast]; 38.9–46.0 h [low-fat breakfast]). Less than dose-proportional increases in maximum plasma concentrations (C_{max}) and area under the concentration–time curve from time 0 to infinity ($AUC_{[0-inf]}$) were observed with ascending eliapixant doses. We observed a pronounced food effect with the high-fat breakfast (4.1-fold increased C_{max} ; 2.7-fold increased $AUC_{[0-inf]}$), a smaller food effect with the low-fat breakfast and a mild-to-moderate effect of itraconazole coadministration on eliapixant (1.1–1.2-fold increased C_{max} ; 1.7-fold increased AUC from 0 to 72 h). Eliapixant was well tolerated with minimal impact on taste perception.

Conclusion: The PK profile, particularly the long half-life, and favourable tolerability with no taste-related adverse events, supports the further development

Dr Isabella Gashaw is now affiliated with Boehringer Ingelheim, Ingelheim am Rhein, Germany

Dr Xinying Chang is now affiliated with Merck Serono, Beijing, China

The authors confirm that the principal investigator for this paper was Sybille Baumann, MD (CRS Clinical Research Services Berlin GmbH, Berlin, Germany), who was responsible for the study and had clinical responsibility for participants

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of eliapixant in disorders with underlying P2X3 receptor-mediated neuronal hypersensitisation.

KEYWORDS

dysgeusia, P2X3 receptor antagonists, pharmacokinetics, taste perception

1 | INTRODUCTION

Adenosine triphosphate is a ubiquitous neurotransmitter acting via ligand-gated P2X receptors^{1,2} and G-protein-coupled P2Y receptors.^{1,2} The P2X receptor is an ion channel consisting of 2 transmembrane domains.¹⁻⁴ Seven subtypes of the P2X receptor are known, numbered P2X1 to P2X7, which can combine as homotrimers (e.g., P2X3) or heterotrimers (e.g., P2X2/3).¹⁻⁴

Overactivity of adenosine triphosphate signalling via P2X3 homotrimeric receptors, expressed predominantly and selectively in C- and A δ -fibre primary afferent neurons, has been implicated in many disorders characterised by neuronal hypersensitisation, including neurogenic inflammation, refractory chronic cough (RCC), overactive bladder and endometriosis-related pain.⁵⁻¹¹ P2X3 receptor antagonists that block overactivation of these neurons could therefore offer a new approach to the management of many of these conditions.⁶

Gefapixant, developed by Merck, initially established proof-of-concept for the targeting of P2X3 in patients with RCC; however, gefapixant produces reversible and selective P2X3 and P2X2/3 receptor antagonism,¹² and taste-related adverse events (AEs) were common with this agent.¹³⁻¹⁷ These taste-related AEs have since been attributed to off-target effects on the P2X2/3 heterotrimer receptor, which is involved in taste perception.¹⁸

Eliapixant is a potent and selective P2X3 receptor antagonist under investigation to reduce neuronal hypersensitisation in RCC (NCT03310645) and overactive bladder (NCT04545580), as well as pain associated with endometriosis (NCT04614246). Here we describe a 2-part, first-in-human, placebo-controlled phase I study (NCT02817100) investigating the tolerability, safety and pharmacokinetics (PK) including dose proportionality of eliapixant, in addition to the effect of food and coadministration with a CYP3A inhibitor, **itraconazole**.

2 | METHODS

2.1 | Objectives, study design and procedures

This study was a 2-part, single-centre, randomised, placebo-controlled, double-blind, parallel-group single-dose escalation study with a fixed-sequence re-dosing approach to investigate the effect of food and itraconazole, a strong cytochrome P450 3A4 inhibitor, on the PK of eliapixant. Part 1 of the study was to investigate the PK, safety and tolerability (including taste assessment) of single ascending

What is already known about this subject

- P2X3 receptors are important mediators of neuronal hypersensitisation in several disorders.
- Gefapixant is a selective P2X3 antagonist, that also causes P2X2/3-receptor antagonism, and causes taste disturbances.

What this study adds

- Eliapixant, a selective P2X3 antagonist, was well tolerated in healthy male subjects, with minimal impact on taste perception.
- Eliapixant had a long half-life, with a pronounced food effect observed with the investigated formulation.

doses of eliapixant or placebo administered under fasted conditions, and with either a high-fat, high-calorie (American) breakfast or itraconazole. Part 2 of the study was added as a protocol amendment after completion of Part 1, in which nonlinearity and an effect of food on eliapixant PK were observed. The objectives of Part 2 were to confirm the food effect at additional doses, and also to investigate meals with lower fat content to characterise the influence of the meal composition on eliapixant PK. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonisation guidelines on Good Clinical Practice. All subjects provided written, informed consent before any study-specific tests or procedures were done.

In Part 1, single ascending doses of immediate-release eliapixant 10–800 mg tablets or identical placebo were administered orally under fasted conditions (Figure 1A). An interval of ≥ 1 week between dose escalations was used for the first 3 dose levels (10, 25 and 50 mg) and ≥ 2 weeks for the subsequent dose levels (100, 200, 400 and 800 mg). Progression to the next highest dose level occurred only after careful assessment of safety and tolerability (at all dose levels) and PK (from 50 mg onwards) of the previous dose level by the principal investigator (blinded) and the sponsor's safety assessment group (unblinded).

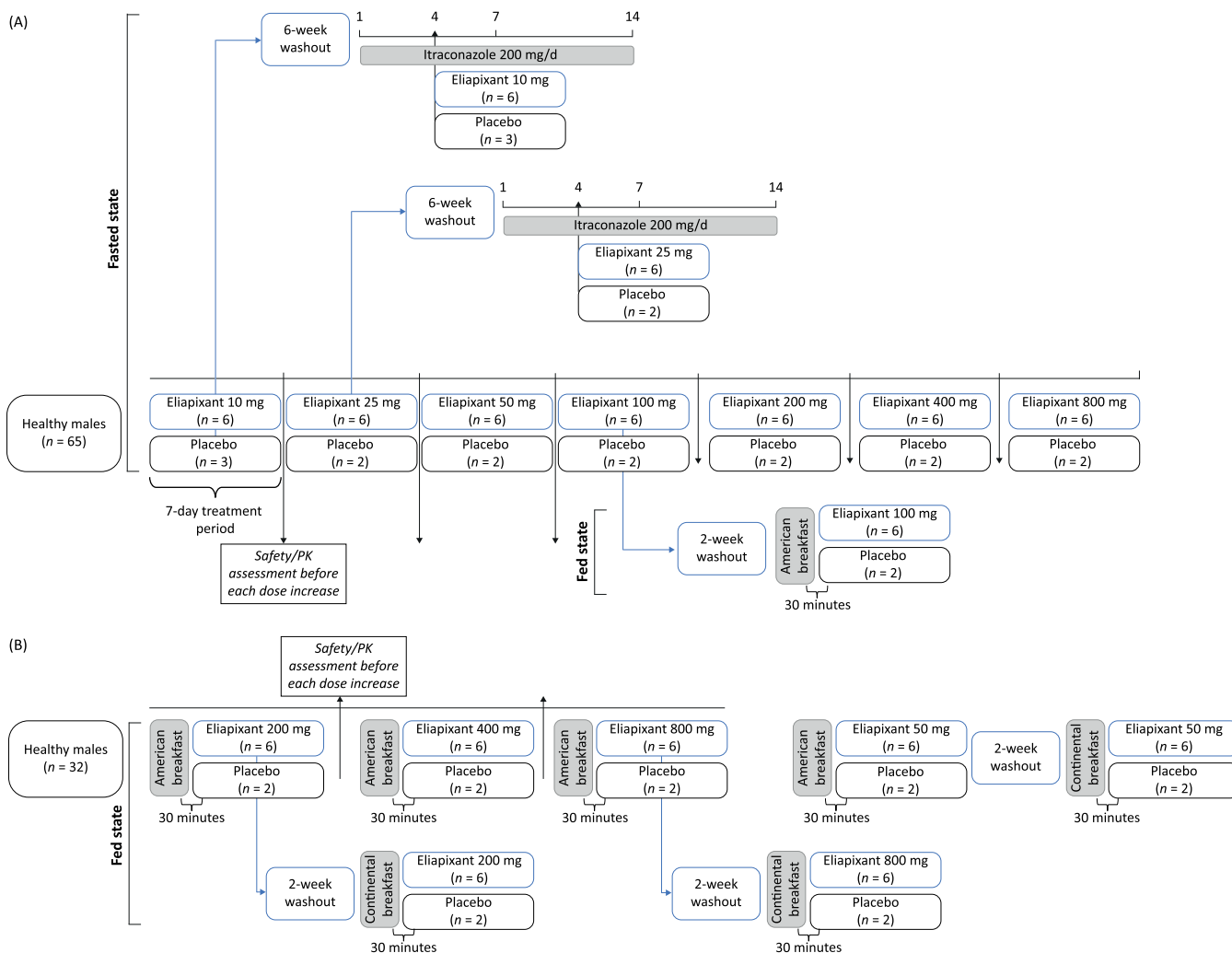


FIGURE 1 Study design of (A) Part 1 and (B) Part 2. PK, pharmacokinetic

For the drug-interaction assessment, the 6 subjects in the eliapiixant 10 and 25 mg and parallel placebo groups received the respective eliapiixant dose or placebo and then, following a ≥ 6 -week washout period, subjects received 200 mg oral itraconazole once daily for 14 days, with a single dose of eliapiixant 10 mg, 25 mg or placebo administered on Day 4 under fasted conditions (Figure 1A).

To assess the food effect, the 6 subjects in the 100 mg eliapiixant and parallel placebo group received eliapiixant 100 mg or placebo under fasted conditions and then, following a ≥ 2 -week washout period, received another single dose of eliapiixant or placebo 30 minutes after starting an American breakfast (Figure 1A) consisting of 2 large fried eggs, 2 slices of fried ham, 2 slices of toast and butter, pan-fried potatoes and decaffeinated coffee with milk, providing approximately 42 g protein, 67 g carbohydrate and 64 g fat (1042 kcal).

In Part 2, immediate-release eliapiixant tablets were given as single oral doses of 50, 200, 400 and 800 mg, or placebo, 30 minutes after an American breakfast (Figure 1B). Escalations to each

subsequent dose level were conducted as in Part 1, with an interval of ≥ 2 weeks and accompanying assessment between progression. After a ≥ 2 -week washout period, subjects treated with eliapiixant 50, 200 and 800 mg were re-dosed with the same single dose following a continental breakfast consisting of 2 bread rolls, jam, cheese, butter and decaffeinated coffee with milk, providing approximately 22 g protein, 69 g carbohydrate and 32 g fat (671 kcal).

2.1.1 | Materials

Eliapixant was administered as immediate-release tablets in strengths of 10, 25 and 150 mg (Bayer AG, Berlin, Germany). Tablet formulations for each dose strength of eliapiixant or placebo were identical in size, shape, colour and smell, and the packaging and labelling were designed to maintain blinding to both site staff and subjects.

Itraconazole (Sempera, Janssen-Cilag Ltd, High Wycombe, UK), was provided in a 10 mg/mL oral solution.

2.2 | Subjects

Eligible subjects were healthy men, based upon a complete medical history, including a physical examination and vital signs (blood pressure, heart rate, electrocardiogram and clinical laboratory tests), of white ethnicity, aged 18–45 years, with a body mass index of 18–30 kg/m², who smoked <10 cigarettes/d. Subjects and their female partners of childbearing potential were required to use an accepted method of contraception for the duration of the study. Confirmation of health insurance coverage was obtained from all subjects before the first screening visit. Subjects who could not taste at least the second highest concentration of each taste quality using the taste strips were excluded. Other key exclusion criteria included relevant diseases, including a medical history of hypogeusia or dysgeusia and existing diseases requiring medication or diseases that could affect metabolism. A full list of exclusion criteria is provided in Table S1.

2.3 | Assessments

Blood samples for determination of eliapixant administered in the fasted state (treatment period 1) or with food (treatment period 2) were taken at baseline (30 minutes before dosing), at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 15 and 24 hours, and on Days 2, 3, 4 and 6 after dosing. For the interaction assessment with itraconazole (treatment period 2), additional blood samples for determination of eliapixant were taken on Days 8, 9 and 11. Samples for determination of itraconazole were taken 3 days, 2 days, 1 day and 1.5 hours before, and then at 1, 2 and 4 hours, and on Days 2, 4, 8 and 11.

For the detection of eliapixant in urine, urine collection was conducted over 24 hours in intervals of 0–6, 6–12 and 12–24 hours after dosing. Concentrations of eliapixant and itraconazole were measured using validated high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS) methods.

Eliapixant was determined in plasma after protein precipitation with acetonitrile containing a stable isotope labelled internal standard followed by separation and detection employing HPLC–MS. The calibration range of the procedure was from 0.50 (lower limit of quantification [LoQ]) to 2000 µg/L (upper LoQ). Mean interassay accuracy of back-calculated concentrations (except lower LoQ) in calibrators ranged from 94% to 102% and precision was ≤5%. Accuracy and precision at the lower LoQ were 100% and 4%, respectively. Quality control samples in the concentration range 1.5–1600 µg/L were determined with an accuracy of 94–104% and a precision of 3–7%. All samples were stored at or below –15°C and analysed immediately after receiving the samples (storage stability for matrix, 340 d).

Eliapixant was determined in urine by HPLC–MS after dilution of 1 part urine with 9 parts plasma (matrix adaption) and subsequent protein precipitation with acetonitrile containing the internal standard. The calibration range of the procedure was from 1.00 (lower LoQ) to 2000 µg/L (upper LoQ) related to a mixture of 1 part urine and 9 parts plasma (from 10.0 µg/L [lower LoQ] to 20 000 µg/L [upper LoQ] related to pure urine). Mean interassay accuracy of back-calculated concentrations

(except lower LoQ) in calibrators ranged between 98% and 103% and precision was ≤4%. Accuracy and precision at the lowest calibrator LoQ were equal to 100% and 4%, respectively. Quality control samples in the concentration range 30–16 000 µg/L related to pure urine were determined with an accuracy of 96–99% and a precision of 4–8%.

Itraconazole was also determined in plasma by HPLC–MS after protein precipitation with acetonitrile. The calibration range was from 1.00 µg/L (lower LoQ) to 1000 µg/L (upper LoQ). Mean interassay accuracy of back-calculated concentrations in calibrators ranged between 98% and 102% and precision was ≤3%. Quality control samples in the concentration range 3.0–750 µg/L were determined with an accuracy of 96–99% and a precision of 2–4%.

Tolerability and safety were assessed by continuously monitoring AEs and use of concomitant medication, in addition to blood pressure, heart rate, electrocardiogram and clinical laboratory tests (see Table S2 for timings).

Taste assessments using taste strips and a dysgeusia questionnaire were performed during the ascending-dose phase of Part 1. Taste strip tests were performed predosing (in the fasted state) and then prior to lunch, 3 hours postadministration, with a follow-up test on Day 6 using taste strips (Burghart Messtechnik GmbH, Wedel, Germany) validated for ascertaining tasting performance,^{19,20} and with the following concentrations: sweet, 0.05–0.4 g/mL sucrose; sour, 0.05–0.3 g/mL citric acid; salty, 0.016–0.25 g/mL sodium chloride; and bitter, 0.0004–0.006 g/mL quinine hydrochloride. The dysgeusia questionnaire was developed by Dr Thomas Hummel (Smell & Taste Clinic, TU Dresden, Germany) and comprised 5 questions assessing type of taste sensation (e.g., sweet, salty, sour or bitter), change and extent of dysgeusia (e.g., no change to complete loss of taste sensation) and sensations in the mouth (e.g., dryness, burning or sour/bitter taste). The questionnaire was administered predosing, then following lunch, 6 hours postadministration, with a follow-up test on Day 6.

2.4 | Data and statistical analyses

No formal statistical sample size estimation was performed for this exploratory study. Based on experience, sample sizes of 8 subjects (eliapixant, $n = 6$; placebo, $n = 2$) per dose level for the single-ascending-dose assessment, 12 subjects for the drug-interaction evaluation (eliapixant 10 and 25 mg plus itraconazole) and 6 subjects for the food effect study were considered sufficient for fulfilling the objectives of the study.

All subjects who received at least 1 dose of any of the study medication were included in the safety analysis set. Evaluation of taste was conducted in the per protocol set, which included all subjects who received at least 1 dose of eliapixant or placebo and had no protocol deviations. PK parameters were evaluated in all subjects who received at least 1 dose of eliapixant and had no protocol deviations affecting the PK analysis.

PK parameters were calculated by the model-independent (compartment-free) method using the program WinNonlin version 5.3 (Pharsight Corporation, St. Louis, MO, USA), with the Automation

Extension (version 2.90, Bayer Pharma AG, Wuppertal, Germany). Log normalisation was required to address non-normal distribution of data. The main PK parameters assessed were maximum plasma concentration (C_{\max}) and area under the concentration–time curve (AUC) from time 0 to infinity ($AUC_{[0-\infty]}$). The results also report AUC for 0 to 72 hours ($AUC_{[0-72]}$) since, especially with the 10-mg dose, eliapixant concentrations dropped below the lower LOQ early and thus $AUC_{[0-72]}$ was considered more reliable. $AUC_{[0-\infty]}$ and $AUC_{[0-72]}$ were also calculated for the food effect and drug interaction. Additional parameters included dose-normalised $AUC_{[0-\infty]}$ ($AUC_{[0-\infty]}/\text{dose [D]}$) and C_{\max} (C_{\max}/D), AUC from time 0 to the final sampling time above the lower limit of quantification ($AUC_{[0-t_{\text{last}}]}$), time to reach maximum plasma concentration (t_{\max}), terminal half-life ($t_{1/2}$), time of last observed concentration value above LOQ (t_{last}), total body clearance of drug calculated after extravascular administration (CL/F), and apparent volume of distribution during terminal phase after extravascular administration (V_z/F).

Analysis of dose proportionality was performed separately under fasted conditions, in the 50-, 100-, 200-, 400- and 800-mg dose groups after an American breakfast, and in the 50-, 200- and 800-mg dose groups after a continental breakfast. For each treatment, the log-transformed values of $AUC_{[0-\infty]}/D$ and C_{\max}/D of eliapixant in plasma for all subjects of each dose group included in the PK set were analysed by analysis of variance (ANOVA) including the dose levels as fixed effects. For each ANOVA, the point estimates (least squares [LS] means) with 90% confidence intervals (CIs) for the different dose levels were calculated by using the standard deviation (SD) of the corresponding ANOVA and re-transforming the LS means and CIs of the corresponding ANOVA to the original scale. Power models were applied to each group of treatment where linear regressions of dose on the log-transformed values of $AUC_{[0-\infty]}$ and C_{\max} were performed and the point estimates and 90% CIs of the slopes for both linear regressions were used to characterise dose proportionality within each group of treatments.²¹ Dose proportionality over the dose range investigated was declared when the CI of the slope β was contained within the upper and lower limits (β_L , β_U) where $\beta_L = 1 + \ln(0.8)/\ln(\text{max (dose)/min (dose)})$, and $\beta_U = 1 + \ln(1.25)/\ln(\text{max (dose)/min (dose)})$. Data and statistical analyses complied with recommendations for experimental design and analysis in pharmacology.²²

All statistical analyses were exploratory in nature and variables were analysed by descriptive statistical methods. Quantitative data were analysed by summary statistics (mean, SD, median [range]) and frequency tables were generated for qualitative data. PK parameters are expressed as geometric mean (% coefficient of variation), with the exception of t_{\max} and t_{last} , which are expressed as median (range). Statistical evaluation was performed using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA).

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in <http://www.guidetopharmacology.org>

(ion channels) and are permanently archived in the Concise Guide to PHARMACOLOGY 2021/22.²³

3 | RESULTS

3.1 | Subjects

Of 205 initially screened, 88 subjects were randomised to treatment and included in the safety analysis set (Figure 2). The most common reasons for screening failure were laboratory values outside the reference ranges (33 subjects), clinical observations (22 subjects; most commonly systolic blood pressure <100 or >145 mmHg or diastolic blood pressure <60 or >90 mmHg), and failure on the taste test (20 subjects). One subject was excluded from the per protocol set due to missing taste strip data and 65 subjects received eliapixant and were eligible for the PK analysis set. Baseline characteristics were generally similar between analysis sets and treatment groups (Table S3).

3.2 | PK parameters for single ascending doses under fasted conditions

When given as single doses under fasted conditions, geometric mean C_{\max} of eliapixant generally increased with increasing dose over the dose range of 10–800 mg (Table 1 and Figure 3A). Total exposure, as indicated by geometric mean $AUC_{[0-\infty]}$ values, also increased with increasing dose over the dose range of 10–400 mg, but no further increase was observed with 800 mg (Table 1). C_{\max} and $AUC_{[0-\infty]}$ showed a less than dose-proportional increase over the dose range of 10–800 mg (Table 1), with LS mean point estimates of $AUC_{[0-\infty]}/D$ and C_{\max}/D progressively decreasing with increasing dose ($P < .0001$ for both measures; Table S4). It was not possible to establish dose-proportional PK using the power model. The t_{\max} was generally consistent over the dose range and there was no clear relationship between $t_{1/2}$ and dose, although it appeared somewhat shorter with the 10-mg dose and longer with the 800-mg dose. Urinary excretion of eliapixant was negligible.

3.3 | Coadministration with itraconazole

In the drug-interaction assessment under fasted conditions, concomitant administration of eliapixant with itraconazole compared with eliapixant alone resulted in a median t_{\max} that was ~1 hour later, a 1.1–1.2-fold higher geometric mean C_{\max} (Table 1 and Figure 3B) and a 1.7-fold (90% CI 1.4–2.1) increase in $AUC_{[0-72]}$ as measured by the LS mean point estimates from the linear mixed model analysis (Table S5). Moreover, $t_{1/2}$ of eliapixant with itraconazole was 1.4–3.7-fold longer than eliapixant administered alone (Table 1). Plasma concentrations of itraconazole over time are shown in Figure S1.

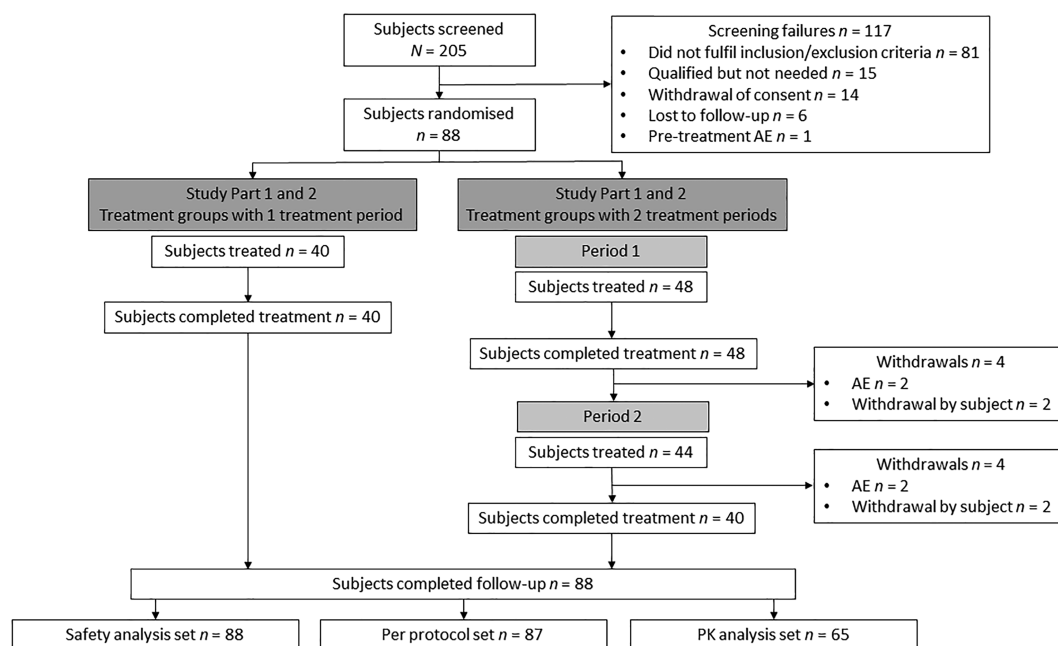


FIGURE 2 Subject disposition. AE, adverse event; PK, pharmacokinetic

3.4 | Food effect

The PK parameters for eliapixant 200 mg illustrate how exposure increased in the fed state, with geometric mean values for C_{max} and $AUC_{[0-inf]}$ increasing 2.6- and 1.9-fold, respectively, following a continental breakfast and 4.1- and 2.7-fold, respectively, following an American breakfast (Table 2, Figures 3C and 4). Similar increases in eliapixant exposure were seen across all doses assessed, with larger increases observed for geometric mean C_{max} (2.7–4.6-fold) and geometric mean $AUC_{[0-inf]}$ (2.4–3.6-fold) following an American breakfast compared with a continental breakfast (geometric mean C_{max} , 2.0–3.3-fold; geometric mean $AUC_{[0-inf]}$, 1.9–2.1-fold; Table S6, Figures S2 and S3). The point estimates for all ratios in the mixed model confirmed that consumption of an American or continental breakfast increased exposure (C_{max} and $AUC_{[0-inf]}$) of eliapixant at all investigated doses (Table S7). The t_{max} was in the same range following an American or continental breakfast with the eliapixant 50- and 200-mg doses, but tended to be shorter when the 800-mg dose was given with a continental breakfast compared with an American breakfast (Table S6).

3.5 | Safety

Overall, 41 of the 88 subjects (47%) experienced at least 1 AE, of whom 23 (26%) experienced an AE considered by the investigator to be related to eliapixant. All eliapixant-related events were mild ($n = 21$; 24%) or moderate ($n = 2$; 2%) in severity, no serious AEs or AE-related deaths were reported during the study and no subjects discontinued eliapixant due to an AE. Overall, the most frequently occurring AEs were:

- Headache ($n = 10$; 11%)
- Blood creatine kinase (CK) increase ($n = 9$; 10%)
- Diarrhoea ($n = 6$; 7%)
- Viral upper respiratory tract infection ($n = 5$; 6%)
- Neutrophil count increase ($n = 4$; 5%)
- Nausea, alanine transaminase increase and oropharyngeal pain (each $n = 3$; 3%)
- Vomiting, fatigue, blood bilirubin increase, white blood cells increased, myalgia and dizziness (each $n = 2$; 2%).

Some subjects received >1 regimen, therefore the numbers experiencing AEs during the various parts of the study may not correspond to the totals above.

This study used an upper limit of normal of 171 U/L for CK. The increase in CK was classified as mild in 8 patients (9%) and moderate in 1 patient (1%). In the latter patient the maximum CK level recorded was 1669 U/L ($9.8 \times$ upper limit of normal) on Day 6 after taking the first dose of eliapixant 50 mg with an American breakfast. This patient reported aching muscles in both legs, which was mild in intensity, lasted for 6 days and was not considered related to eliapixant. No CK levels >800 U/L were recorded in any other patient. Table 3 summarises AEs for administration of eliapixant doses alone under fasted conditions; AEs following dosing with eliapixant and concomitant itraconazole and eliapixant following food are shown in Table S8.

Overall taste scores showed no impact of eliapixant on perception of taste sensation following dosing either under fasted conditions or following an American breakfast (Figure 5). Patient-reported outcomes from the dysgeusia questionnaire suggested taste dysfunction in 1 subject dosed with eliapixant 800 mg following an American breakfast. This subject reported dysgeusia with a

TABLE 1 Summary of plasma PK parameters for single doses of eliapixant taken under fasted conditions and when coadministered with ITZ

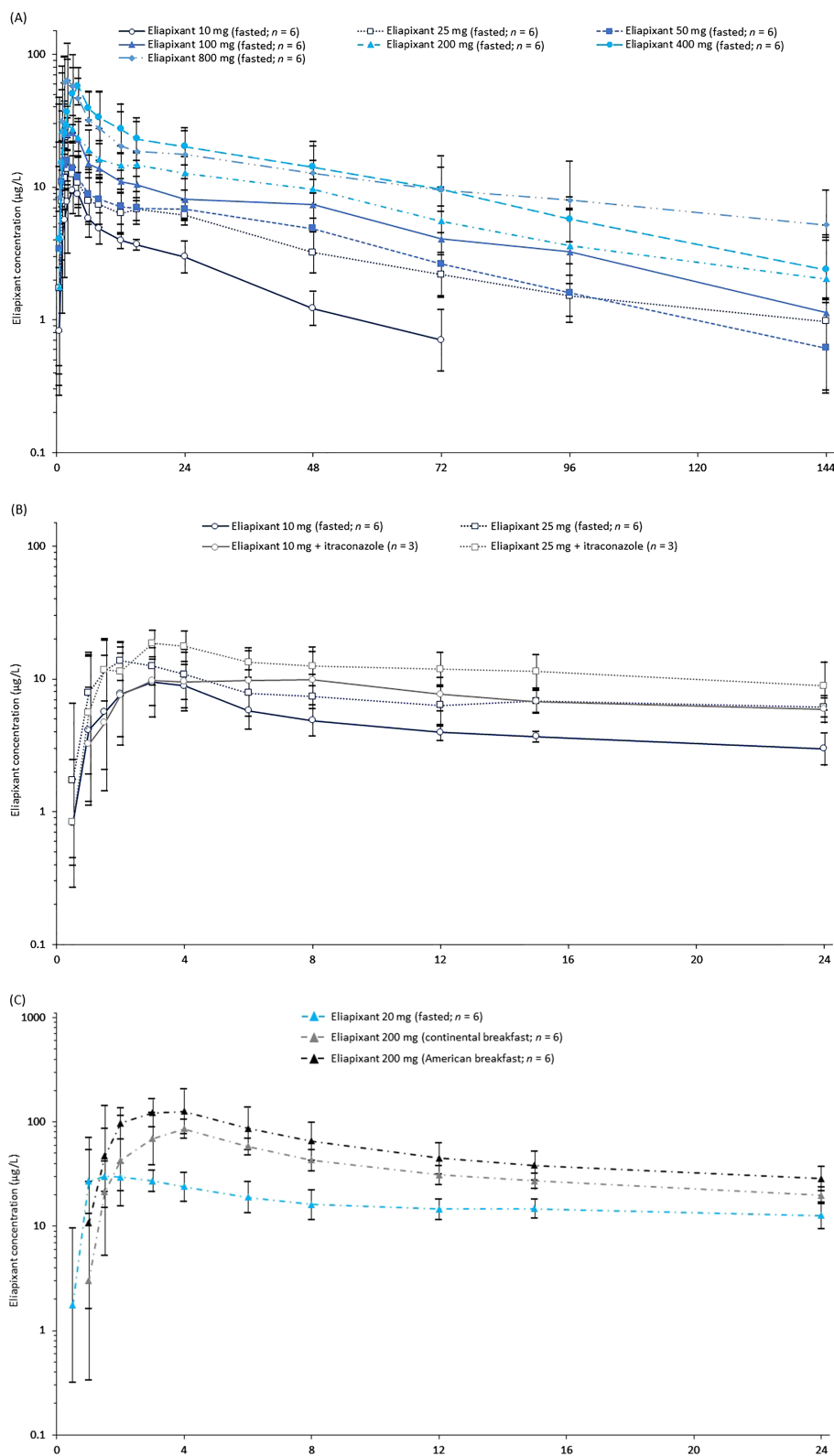
	Eliapixant under fasted conditions						Eliapixant + ITZ		
	10 mg (n = 6)	25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	400 mg (n = 6)	800 mg (n = 6)	10 mg (n = 3)	25 mg (n = 5)
C_{max} ($\mu\text{g/L}$)	12.6 (34.1)	16.2 (21.4)	17.0 (44.5)	32.6 (24.6)	36.8 (38.6)	67.6 (41.4)	77.2 (29.7)	14.1 (34.6)	20.1 (25.3)
C_{max}/D ($10^{-3}/\text{L}$)	1.26 (34.1)	0.65 (21.4)	0.34 (44.5)	0.33 (24.6)	0.18 (38.6)	0.17 (41.4)	0.10 (29.7)	1.41 (34.6)	0.80 (25.3)
$AUC_{[0-\text{inf}]}$ ($\mu\text{g h/L}$)	207 (17.0) ^a	473 (24.0) ^b	588 (27.4)	748 (35.8) ^b	1120 (33.8) ^a	1950 (38.1)	1900 (33.0)	599 (10.5)	990 (80.1) ^b
$AUC_{[0-\text{inf}]/D}$ (10^{-3} h/L)	20.7 (17.0) ^a	18.9 (24.0) ^b	11.8 (27.4)	7.48 (35.8) ^b	5.62 (33.8) ^a	4.86 (38.1)	2.37 (33.0) ^b	59.9 (10.5)	18.9 (24.0) ^b
$AUC_{[0-72]}$	187 (11.2)	355 (23.7)	440 (18.3)	642 (27.8)	862 (29.7)	1430 (36.2)	1310 (36.4)	344 (4.8)	564 (37.9)
$AUC_{[0-\text{last}]}$ ($\mu\text{g h/L}$)	198 (22.2)	459 (26.3)	535 (26.2)	834 (45.0)	1120 (36.6)	1800 (36.8)	1880 (39.4)	519 (11.6)	919 (61.7)
t_{max} (h), median (range)	2.02 (1.53–4.07)	1.78 (1.00–3.00)	2.00 (1.00–6.00)	1.75 (1.00–4.02)	1.50 (1.00–3.00)	2.98 (1.50–8.00)	1.75 (1.50–3.00)	3.00 (2.92–8.00)	3.00 (1.50–4.0)
$t_{1/2}$ (h)	23.5 (31.1) ^a	49.4 (22.2) ^b	36.5 (36.2)	32.9 (14.1) ^b	40.9 (21.3) ^a	38.1 (18.8)	58.9 (21.5) ^b	85.8 (10.4)	69.1 (84.1) ^b
CL/F (L/h)	48.2 (17.0) ^a	52.8 (24.0) ^b	85.0 (27.4)	134 (35.8) ^b	178 (33.8) ^a	206 (38.1)	421 (33.0) ^b	16.7 (10.5)	25.2 (80.1) ^b
V_z/F (L)	1630 (15.8) ^a	3770 (43.8) ^b	4480 (32.7)	6350 (24.3) ^b	10 500 (39.8) ^a	11 300 (39.6)	35 800 (51.0) ^b	2060 (21.1)	2520 (50.3) ^b
t_{last} (h), median (range)	83.6 (47.7–144)	144 (144–145)	144 (95.4–144)	144 (96.3–145)	144 (144–144)	144 (143–145)	144 (144–145)	216 (216–216)	264 (95.7–264)

Data are expressed as geometric mean (% coefficient of variation) unless otherwise specified. $AUC_{[0-72]}$, area under the concentration–time curve from 0 to 72 hours; $AUC_{[0-\text{inf}]}$, area under the concentration–time curve from time 0 to infinity; $AUC_{[0-\text{last}]}$, area under the concentration–time curve from time 0 to t_{last} ; $AUC_{[0-\text{inf}]/D}$, dose-normalised area under the concentration–time curve from time 0 to infinity; CL/F, total body clearance of drug calculated after extravascular administration; C_{max} , maximum plasma concentration; C_{max}/D , dose-normalised maximum plasma concentration; ITZ, itraconazole; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; t_{last} , time of the last data point above the lower limit of quantification; t_{max} , time to reach maximum plasma concentration; V_z/F , apparent volume of distribution during terminal phase after extravascular administration.

^an = 5.

^bn = 4.

FIGURE 3 Concentration–time profiles of eliapixant in plasma (geometric mean \pm standard deviation semi-logarithmic scale): (A) after a single oral dose of 10–800 mg administered alone under fasted conditions; (B) over 24 hours after a single oral dose of 10 or 25 mg administered alone or in combination with itraconazole under fasted conditions; (C) over 24 hours after a single oral dose of 200 mg under fasted conditions, or following an American or continental breakfast



reduction in salty and bitter taste sensations. However, the reported dysgeusia was not supported by taste strip evaluation, where no marked differences in taste sensitivity were observed; the taste effect in this subject was not apparent at the 6-day follow-up taste test.

4 | DISCUSSION

This first-in-human phase I study investigated the tolerability, safety and PK of oral doses of eliapixant, a potent and selective P2X₃ receptor antagonist, in addition to assessing dose proportionality and the

	Fasted 200 mg (n = 6)	Continental breakfast 200 mg (n = 6)	American breakfast 200 mg (n = 6)
C_{max} ($\mu\text{g/L}$)	36.8 (38.6)	94.2 (21.3)	151 (28.4)
$AUC_{[0-\infty]}$ ($\mu\text{g h/L}$)	1120 (33.8) ^a	2080 (19.3)	3050 (44.8)
$AUC_{[0-t_{last}]}$ ($\mu\text{g h/L}$)	1120 (36.6)	1910 (14.7)	2770 (40.1)
$AUC_{[0-72]}$ ($\mu\text{g h/L}$)	862 (29.7)	1542 (10.9)	2279 (32.0)
t_{max} (h), median (range)	1.50 (1.00–3.00)	3.94 (1.50–6.00)	3.50 (1.50–4.00)
$t_{1/2}$ (h)	40.9 (21.3) ^a	38.8 (33.2)	40.4 (39.5)

Data are expressed as geometric mean (% coefficient of variation) unless otherwise specified.

$AUC_{[0-72]}$, area under the concentration–time curve from time 0 to 72 hours; $AUC_{[0-\infty]}$, area under the concentration–time curve from time 0 to infinity; $AUC_{[0-t_{last}]}$, area under the concentration–time curve from time 0 to the last data point above the lower limit of quantification; C_{max} , maximum plasma concentration; PK, pharmacokinetic; $t_{1/2}$, terminal half-life; t_{max} , time to reach maximum plasma concentration.

^an = 5.

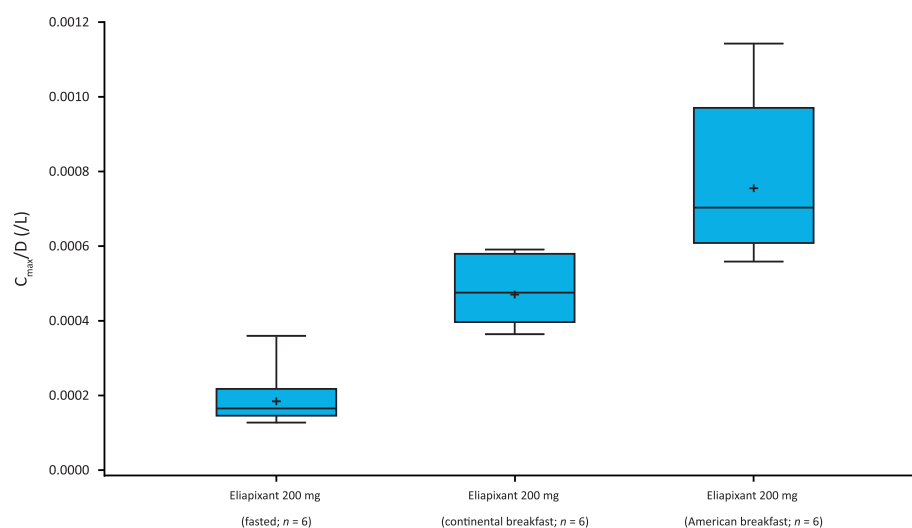


TABLE 2 Summary of plasma PK parameters for eliapixant 200 mg under fasted conditions or with either an American or continental breakfast

FIGURE 4 Box plot for dose-normalised maximum concentration of eliapixant 200 mg in plasma given under fasted conditions or after an American or continental breakfast. The box represents the 25th to 75th percentile, the horizontal line represents the median, the cross is the geometric mean and the vertical lines extend from the box as far as the data extends, including outliers. C_{max}/D , dose-normalised maximum plasma concentration

effects of coadministration with food and itraconazole on relative bioavailability of eliapixant in healthy men.

When ascending single doses of immediate-release eliapixant 10–800-mg tablets were administered under fasted conditions, there was a less than dose-proportional increase in C_{max} and $AUC_{[0-\infty]}$, with no further increase in exposure, as measured by $AUC_{[0-\infty]}$, at the 800-mg dose. These observations may be due to incomplete solubility of the eliapixant formulation in the gastrointestinal tract, leading to decreasing bioavailability with increasing doses. However, based on dissolution data available at the time and bioavailability studies in rats (Bayer AG, data on file), no dissolution-related nonlinearity in exposure was expected. Of note, eliapixant had a long $t_{1/2}$, which has implications for dosing and risk of taste AEs. A long $t_{1/2}$ is expected to lead to high accumulation, which has since been confirmed in subsequent studies, and low fluctuation in drug concentration at steady state. This would result in concentrations staying above the predicted therapeutic threshold of 80% receptor occupancy (RO80), while staying below concentrations leading to taste-related AEs (data on file, Bayer AG). Conversely, a P2X3 antagonist with a short $t_{1/2}$ would

have to be given at higher doses to maintain \geq RO80 with the downside of high maximum concentrations possibly increasing the risk of taste-related AEs.

Food had a pronounced effect on eliapixant exposure with substantially higher C_{max} , increased $AUC_{[0-\infty]}$ and longer t_{max} when given after an American breakfast compared with fasted conditions. C_{max} and $AUC_{[0-\infty]}$ were also increased after a continental breakfast compared with fasted conditions, but to a lesser extent than after an American breakfast. The food effect was not expected on the basis of preclinical dissolution data and studies in dogs, in which no effect of food on exposure was seen (Bayer AG, data on file). As with the nonlinear PK findings, the food effect observed is probably due to incomplete solubility of the eliapixant formulation, which may be enhanced when taken with a high- or moderate-fat meal. In the drug–interaction assessment, a mild-to-moderate effect on PK was observed when eliapixant was coadministered with the strong CYP3A4 inhibitor itraconazole, with approximately a 2-fold increase in total exposure. Exposure to itraconazole in the current study was consistent with previously published PK data for itraconazole.²⁴ Based

TABLE 3 Summary of AEs in subjects receiving eliapixant or placebo under fasted conditions

	Eliapixant							Placebo (n = 15)
	10 mg (n = 6)	25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	400 mg (n = 6)	800 mg (n = 6)	
Any AE	2 (33)	1 (17)	4 (67)	3 (50)	1 (17)	3 (50)	3 (50)	4 (27)
Any eliapixant-related AE	1 (17)	0	3 (50)	2 (33)	0	1 (17)	2 (33)	3 (20)
Mild intensity	1 (17)	0	3 (50)	2 (33)	0	1 (17)	2 (33)	3 (20)
Moderate intensity	0	0	0	0	0	0	0	0
Any SAE	0	0	0	0	0	0	0	0
AE-related death	0	0	0	0	0	0	0	0
Discontinuation of eliapixant due to AEs	0	0	0	0	0	0	0	–
Most common AEs ^a								
Headache	1 (17)	1 (17)	3 (50)	0	0	0	0	2 (13)
Blood creatine kinase increased	0	0	1 (17)	1 (17)	0	0	0	0
Diarrhoea	0	0	0	0	0	0	1 (17)	0
Viral upper respiratory tract infection	0	0	0	0	0	0	1 (17)	1 (7)

Data are expressed as n (%).

AE, adverse event; SAE, serious adverse event.

^aAEs occurring in >5% of subjects overall (including fasted state, in the presence of itraconazole, and after an American or continental breakfast; Table S8).

on the current results, no restrictions in the use of eliapixant with CYP3A4 inhibitors would be expected; however, concomitant safety and efficacy need to be shown in larger patient trials.

Overall, eliapixant was well tolerated at all doses administered, with no serious AEs. Eliapixant also had minimal impact on perception of taste following single-dose administration of up to 800 mg, reflecting the high selectivity that eliapixant has for the P2X3 receptor and its PK profile. The first postdose taste tests were administered 3 hours postdosing, which was within 1 SD of t_{max} under fasted conditions, or very close to t_{max} under fed conditions, yet there was no clear difference in response compared with the baseline tests. Findings from the proof-of-concept studies with eliapixant, which commenced following the research described here, are consistent with these early observations that eliapixant appears to have fewer taste-related AEs than observed with nonselective P2X3 and P2X2/3 receptor antagonism.^{13–17,25,26} A multiple-dose PK study of eliapixant 10–750 mg in healthy volunteers showed no clinically relevant effects on taste perception, in addition to a less than dose-proportional increase in exposure with increasing dose.²⁵ Furthermore, in a phase II study, eliapixant was well tolerated in patients with RCC, with a lower incidence of taste-related AEs (8–21% of patients)²⁶ than has previously been reported for gefapixant (up to 80% of patients with 50 mg twice daily) in RCC.^{15,16} It is possible that a lower incidence of taste disturbances in healthy volunteers compared with patients may be due to a higher sensitivity in patients, although a study evaluating gefapixant in healthy volunteers and patients with chronic cough showed a numerically higher incidence of dysgeusia and ageusia in the healthy volunteers.¹⁴ It is also feasible that fewer AEs were

observed with eliapixant in healthy volunteers than in patients with RCC because of the smaller populations evaluated.

It is likely that the lower incidence of taste-related AEs with eliapixant compared with gefapixant is due to the selective P2X3 receptor antagonism with eliapixant, which, with low predicted clearance and higher safety margin, may ultimately offer an alternative approach to the inhibition of afferent neuronal hypersensitisation. The PK data from this study, particularly the long $t_{1/2}$, and the AE profile support the further development of eliapixant in relevant patient populations where overactivity of P2X3 receptors has been implicated in their pathogenesis, such as RCC, endometriosis and overactive bladder. The formulation tested here was suitable for early studies (phase I and IIa), but a formulation without a relevant food effect and high bioavailability is necessary for later trials (phase IIb onwards) and ultimately clinical use. Comprehensive preclinical and clinical research into an improved formulation without a relevant food effect has therefore been conducted.

Several limitations should be considered when interpreting the results of this study. Typical for a study of this type, sample sizes were small and included male, white subjects only. While the screening failure rate of ~60% was not unusual for a study in healthy volunteers, the taste assessment was an additional screening step compared with healthy volunteer studies in general, and inability to taste the strips made a significant contribution to screening failure. There was a high subject dropout due to the extended period (≥ 6 wk) between dose and re-dose in the itraconazole treatment group. This delay in re-dosing reflected the less than dose-proportional increase in $AUC_{[0-inf]}$, which meant that data from the higher dose levels were required to

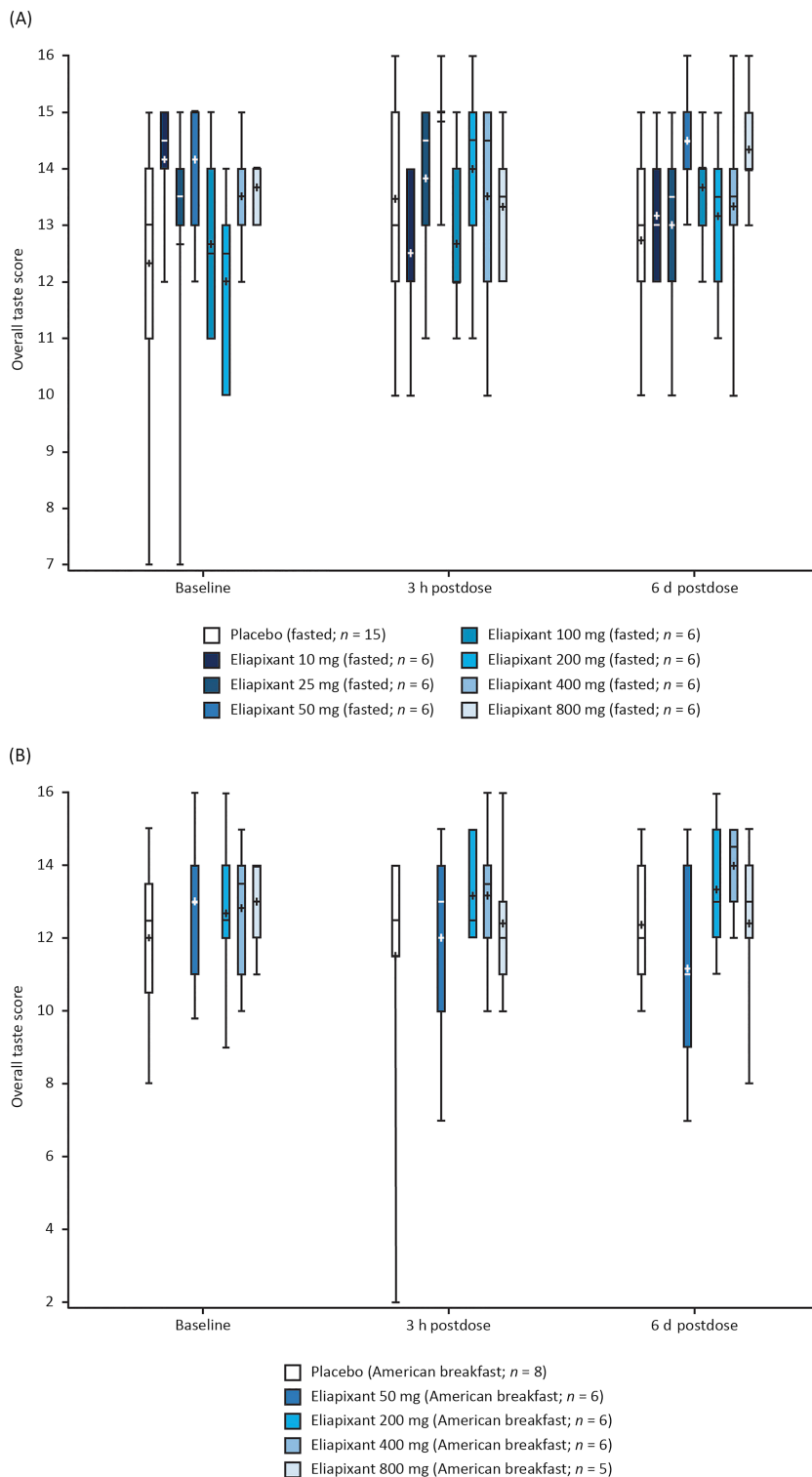


FIGURE 5 Boxplots of overall taste score prior to dosing and 3 hours and 6 days following eliapixant in the (A) fasted and (B) fed (American breakfast) states. The boxes describe the IQR, with median (line) and geometric mean (+). The whiskers delineate $1.5 \times$ IQR. IQR, interquartile range

ensure the expected increase in systemic exposure with itraconazole had been assessed under fasted conditions in order to establish a safety window for subsequent itraconazole coadministration. Furthermore, taste was assessed in healthy subjects only, and further studies with patients with relevant conditions will confirm whether the observed minimal impact on taste perception also translates to relevant patient populations.

Overall, eliapixant was well tolerated in single oral doses of 10–800 mg given under fasted conditions or following food and there was little evidence of a clinically relevant effect on PK when given concomitantly with itraconazole. Importantly, reflecting both its high selectivity for the P2X₃ receptor and its PK profile, eliapixant had minimal impact on perception of taste. The findings from this first-in-human study therefore support the further ongoing clinical

development of eliapixant for use in various conditions mediated through P2X3 receptors.

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COMPETING INTERESTS

Stefan Klein, Uwe Thuß and Christian Friedrich are employees of Bayer AG, Berlin, Germany. Sybille Baumann is an employee of CRS Clinical Research Services Berlin GmbH. Isabella Gashaw was previously employed by Bayer AG, Berlin, Germany and is now an employee of Boehringer Ingelheim, Ingelheim am Rhein, Germany. Xinying Chang was previously employed by Bayer AG, Berlin, Germany and is now an employee of Merck Serono, Beijing, China. Thomas Hummel, since 2018, has conducted research and received funding from: Sony, Stuttgart, Germany; Smell and Taste Lab, Geneva, Switzerland; Takasago, Paris, France; aspuracip, Berlin, Germany; Baia Foods, Madrid, Spain; Frequency Therapeutics, Farmington, CT, USA.

CONTRIBUTORS

S.K. was involved in study design, data analysis and interpretation; I.G. was involved in study design, data analysis and interpretation; S.B. was involved in data analysis and interpretation; X.C. was involved in study design, data analysis and interpretation; T.H. was involved in data analysis and interpretation; U.T. was involved in data analysis and interpretation; C.F. was involved in study design, data analysis and interpretation. All authors critically reviewed the manuscript and approved the final draft.

DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations and Pharmaceutical Research and Manufacturers of America principles for responsible clinical trial data sharing, pertaining to scope, time point and process of data access. Bayer commits to sharing upon request from qualified scientific and medical researchers, patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union as necessary for doing legitimate research. This commitment applies to data on new medicines and indications that have been approved by the European Union and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymised patient-level data and supporting documents from clinical studies to

do further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsors section of the portal. Data access will be granted to anonymised patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

ORCID

Isabella Gashaw  <https://orcid.org/0000-0001-5984-576X>

Thomas Hummel  <https://orcid.org/0000-0001-9713-0183>

Christian Friedrich  <https://orcid.org/0000-0001-8955-4808>

REFERENCES

- Burnstock G. Purinergic signalling: from discovery to current developments. *Exp Physiol*. 2014;99(1):16-34. doi:10.1113/expphysiol.2013.071951
- Burnstock G. Purine and purinergic receptors. *Brain Neurosci Adv*. 2018;6(2):2398212818817494. doi:10.1177/2398212818817494
- North RA. P2X receptors. *Philos Trans R Soc Lond B Biol Sci*. 2016;371(1700):20150427. doi:10.1098/rstb.2015.0427
- North RA, Surprenant A. Pharmacology of cloned P2X receptors. *Annu Rev Pharmacol Toxicol*. 2000;40(1):563-580. doi:10.1146/annurev.pharmtox.40.1.563
- Burnstock G. Purinergic mechanosensory transduction and visceral pain. *Mol Pain*. 2009;5:69. doi:10.1186/1744-8069-5-69
- Ford AP. In pursuit of P2X3 antagonists: novel therapeutics for chronic pain and afferent sensitization. *Purinergic Signal*. 2012;8(Suppl 1):3-26. doi:10.1007/s11302-011-9271-6
- Cockayne DA, Dunn PM, Zhong Y, et al. P2X2 knockout mice and P2X2/P2X3 double knockout mice reveal a role for the P2X2 receptor subunit in mediating multiple sensory effects of ATP. *J Physiol*. 2005;567(Pt 2):621-639. doi:10.1113/jphysiol.2005.088435
- Fabbretti E. ATP P2X3 receptors and neuronal sensitization. *Front Cell Neurosci*. 2013;7:236. doi:10.3389/fncel.2013.00236
- Bernier LP, Ase AR, Seguela P. P2X receptor channels in chronic pain pathways. *Br J Pharmacol*. 2018;175(12):2219-2230. doi:10.1111/bph.13957
- Song WJ, Morice AH. Cough hypersensitivity syndrome: a few more steps forward. *Allergy Asthma Immunol Res*. 2017;9(5):394-402. doi:10.4168/aaair.2017.9.5.394
- Ding S, Yu Q, Wang J, et al. Activation of ATF3/AP-1 signaling pathway is required for P2X3-induced endometriosis pain. *Hum Reprod*. 2020;35(5):1130-1144. doi:10.1093/humrep/deaa061
- Richards D, Gever JR, Ford AP, Fountain SJ. Action of MK-7264 (gefapixant) at human P2X3 and P2X2/3 receptors and in vivo efficacy in models of sensitisation. *Br J Pharmacol*. 2019;176(13):2279-2291. doi:10.1111/bph.14677
- Abdulqawi R, Dockry R, Holt K, et al. P2X3 receptor antagonist (AF-219) in refractory chronic cough: a randomised, double-blind, placebo-controlled phase 2 study. *Lancet*. 2015;385(9974):1198-1205. doi:10.1016/S0140-6736(14)61255-1
- Morice AH, Kitt MM, Ford AP, et al. The effect of gefapixant, a p2X3 antagonist, on cough reflex sensitivity: a randomised placebo-controlled study. *Eur Respir J*. 2019;54(1):1900439. doi:10.1183/13993003.00439-2019
- Smith JA, Kitt MM, Butera P, et al. Gefapixant in two randomised dose-escalation studies in chronic cough. *Eur Respir J*. 2020;55(3):1901615. doi:10.1183/13993003.01615-2019

16. Smith JA, Kitt MM, Morice AH, et al. Gefapixant, a P2X3 receptor antagonist, for the treatment of refractory or unexplained chronic cough: a randomised, double-blind, controlled, parallel-group, phase 2b trial. *Lancet Respir Med*. 2020;8(8):775-785. doi:[10.1016/S2213-2600\(19\)30471-0](https://doi.org/10.1016/S2213-2600(19)30471-0)
17. McGarvey LP, Birring SS, Morice AH, et al. Efficacy and safety of gefapixant, a P2X(3) receptor antagonist, in refractory chronic cough and unexplained chronic cough (COUGH-1 and COUGH-2): Results from two double-blind, randomised, parallel-group, placebo-controlled, phase 3 trials. *Lancet*. 2022;399(10328):909-923. doi:[10.1016/S0140-6736\(21\)02348-5](https://doi.org/10.1016/S0140-6736(21)02348-5)
18. Garceau D, Chauret N. Blu-5937: A selective P2X3 antagonist with potent anti-tussive effect and no taste alteration. *Pulm Pharmacol Ther*. 2019;56:56-62. doi:[10.1016/j.pupt.2019.03.007](https://doi.org/10.1016/j.pupt.2019.03.007)
19. Mueller C, Kallert S, Renner B, et al. Quantitative assessment of gustatory function in a clinical context using impregnated "taste strips". *Rhinology*. 2003;41(1):2-6.
20. Landis BN, Welge-Luessen A, Brämerson A, et al. "Taste strips" - a rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. *J Neurol*. 2009;256(2):242-248. doi:[10.1007/s00415-009-0088-y](https://doi.org/10.1007/s00415-009-0088-y)
21. Smith BP, Vandenhende FR, DeSante KA, et al. Confidence interval criteria for assessment of dose proportionality. *Pharm Res*. 2000;17(10):1278-1283. doi:[10.1023/A:1026451721686](https://doi.org/10.1023/A:1026451721686)
22. Curtis MJ, Alexander S, Cirino G, et al. Experimental design and analysis and their reporting ii: Updated and simplified guidance for authors and peer reviewers. *Br J Pharmacol*. 2018;175(7):987-993. doi:[10.1111/bph.14153](https://doi.org/10.1111/bph.14153)
23. Alexander SPH, Mathie A, Peters JA, et al. The concise guide to pharmacology 2021/22: Ion channels. *Br J Pharmacol*. 2021;178(S1):S157-S245.
24. Hardin TC, Graybill JR, Fetchick R, Woestenborghs R, Rinaldi MG, Kuhn JG. Pharmacokinetics of itraconazole following oral administration to normal volunteers. *Antimicrob Agents Chemother*. 1988;32(9):1310-1313. doi:[10.1128/AAC.32.9.1310](https://doi.org/10.1128/AAC.32.9.1310)
25. Friedrich C, Francke K, Gashaw I, et al. Safety, pharmacodynamics, and pharmacokinetics of P2X3 receptor antagonist eliapixant (BAY 1817080) in healthy subjects: double-blind, randomized study. *Clin Pharmacokinet*. 2022; In press.
26. Morice A, Smith JA, McGarvey L, et al. Eliapixant (BAY 1817080), a P2X3 receptor antagonist, in refractory chronic cough: a randomised, placebo-controlled, crossover phase 2a study. *Eur Respir J*. 2021;58(5):2004240. doi:[10.1183/13993003.04240-2020](https://doi.org/10.1183/13993003.04240-2020)

SUPPORTING INFORMATION

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