Efficacy and Safety of Eliapixant in Refractory Chronic Cough: The Randomized, Placebo-Controlled Phase 2b PAGANINI Study

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Acknowledgments The authors would like to thank the investigators and participants for their involvement in the study. Julian Borissoff, MD, PhD (Bayer AG, Berlin, Germany) was the Global Clinical Lead mainly responsible for the study design and conduct. Katrin Roth, PhD (Bayer AG, Berlin, Germany) was the responsible statistician during study planning and setup and assisted with statistical analyses and interpretation of data. Medical writing assistance was provided by Rachael Powis, PhD (Adelphi Communications Ltd, Bollington, UK), funded by Bayer AG (Berlin, Germany) in accordance with Good Publications Practice. Recruitment for this study was supported by the NIHR Manchester Clinical Research Facility, UK.

Target Journal	**Lung**
Word/figure/reference limit	**Original research article:** Word limit: 2,600 (flexibility to up to 3,500 words confirmed by journal) Figures limit: 5 Manuscript currently: 3,170 words, 3 figures, 5 tables, 30 references
Abstract limit	250 words (structured) Abstract currently: 246 words.

Abstract

Introduction The PAGANINI study evaluated the efficacy and safety of the selective P2X3 antagonist eliapixant in patients with refractory chronic cough (RCC).

Methods PAGANINI was a randomized, double-blind, parallel-group, placebo-controlled, multicenter, dose-finding, phase 2b study. Adults with RCC lasting ≥12 months and cough severity ≥40 mm on a visual analog scale at screening were enrolled. Participants were randomized 1:1:1:1 to twice-daily 25 mg, 75 mg, or 150 mg oral eliapixant or placebo for 12 weeks. The primary endpoint was change from baseline in 24-hour cough count after 12 weeks of intervention.

Results Overall, 310 participants were randomized to twice-daily eliapixant 25 mg (*n*=75), 75 mg (*n*=78), 150 mg (*n*=80), or placebo (*n*=77). A statistically significant dose–response signal with eliapixant was detected for the primary endpoint (all dose–response models, adjusted $p<0.1$; one-sided). Adverse events (AEs) were reported in 39 (51%) participants with placebo and 43–51 (57–65%) participants receiving eliapixant. The most common AE was dysgeusia, occurring in 1% (*n*=1) of the placebo group and 1–16% (*n*=1–13) of the eliapixant groups in a dose-related manner. One case of a moderate drug-induced liver injury occurred in a participant receiving 150 mg twice-daily eliapixant.

Conclusion Eliapixant demonstrated efficacy and a favorable taste tolerability profile in RCC. However, a drug-induced liver injury contributed to intensified liver monitoring in clinical trials with eliapixant and discontinuation of the entire development program in all indications by Bayer AG.

Clinical Trial Registration ClinicalTrials.gov identifier NCT04562155; registered September 18, 2020

Keywords

Chronic cough · Eliapixant · P2X3 receptor antagonist · Phase 2b clinical trial

Introduction

Chronic cough (CC), estimated to affect around 10% of the global adult population [1], is defined as a cough lasting ≥8 weeks [2]. CC with unexplained underlying etiology or CC that is unresponsive to conventional treatment are jointly referred to here as refractory CC (RCC) [2]. RCC can have a detrimental impact on patients' quality of life (QoL) [3] and mental health [4, 5] and results in significant economic burden, with patients experiencing repeated treatment failures and delayed diagnosis [4]. There are no approved drugs for RCC in countries other than Japan [6] and Switzerland [7], resulting in widespread use of off-label treatment options with limited efficacy and a poor safety profile, and non-pharmacologic interventions [4]. There is therefore a large unmet clinical need for efficacious, well-tolerated therapies.

Neuronal hypersensitivity is implicated in the pathogenesis of RCC [8]. Patients with RCC have increased cough reflex sensitivity, which may result from vagal nerve hypersensitivity or changes in the central nervous system projections and central sensitization as presumed underlying mechanisms [8]. P2X3 receptors are thought to play an important role in sensory neural dysregulation associated with RCC [9, 10]. Preclinical studies have shown that P2X2/3 receptors can regulate afferent sensory adenosine triphosphate-mediated signaling in the vagus nerve [9]. Clinical trials of the P2X3 receptor antagonist gefapixant showed efficacy in objective and subjective measures of cough in patients with RCC [11–13]. However, substantial taste-related tolerability issues [11–13], attributed to the block of P2X2/3 receptors on nerves innervating taste buds [14], may limit acceptance of gefapixant by patients.

Eliapixant is a potent P2X3 receptor antagonist with a good tolerability profile in healthy subjects, and high selectivity over the P2X2/3 receptor in vitro, potentially resulting in fewer off-target effects [15–17]. In a phase 2a study, eliapixant significantly reduced cough frequency and severity in patients with RCC, with a lower rate of taste-related side effects than those observed with therapeutic doses of gefapixant [18]. The aim of the phase 2b

PAGANINI study was to identify the optimal dose of eliapixant in patients with RCC, to further assess efficacy, and to characterize the safety and tolerability profile of eliapixant over 12 weeks.

Methods

Study Design

PAGANINI (ClinicalTrials.gov NCT04562155) was a randomized, double-blind, parallel-group, placebo-controlled, dose-finding efficacy and safety study conducted at 99 centers in 19 countries (see Supplementary Methods for more details). The study consisted of a 14-day screening period, 12 weeks of randomized treatment, and a 30-day safety follow-up (Supplementary Fig. S1). The study protocol and statistical analysis plan are available on ClinicalTrials.gov.

Eligible participants were centrally randomized 1:1:1:1 by the sponsor using block randomization to receive one of three oral doses of twice-daily eliapixant (25 mg, 75 mg, or 150 mg; Bayer AG, Berlin, Germany) or placebo using Interactive Response Technology (IRT version 2.1; Suvoda, USA), stratified by region. To maintain blinding, tablets containing eliapixant and placebo were identical in size, color, and shape.

Ethics Approval and Consent to Participate

The Institutional Review Board/Independent Ethics Committee at each center approved the protocol. The study was carried out in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and the Council for International Organizations of Medical Sciences International Ethical Guidelines. All participants provided written informed consent.

Participants

Adults aged ≥18 years with RCC lasting ≥12 months, with persistent cough for ≥8 weeks before screening, and with cough severity ≥40 mm measured on a 100 mm visual analog scale (VAS) at screening, were enrolled by the investigators. Full inclusion and exclusion criteria are in the Supplementary Methods.

Procedures

Using an ambulatory cough recording device (VitaloJAK, Vitalograph, Ireland [19]), 24-hour cough count monitoring was performed at every visit to Week 12 (see Supplementary Methods for more details). Participants completed the cough severity VAS [20] daily and the Leicester Cough Questionnaire (LCQ) [21] at all visits (see Supplementary Methods for more details). Adverse events (AEs) and other safety outcomes were evaluated throughout the study and at follow-up.

Outcomes

The primary efficacy endpoint was change from baseline in 24-hour cough count after 12 weeks of intervention. Secondary efficacy endpoints included: the percentage of participants with ≥30% reduction from baseline 24-hour cough count after 12 weeks; change from baseline 24-hour cough count after 2, 4, and 8 weeks; change from baseline awake cough count per hour after 2, 4, 8, and 12 weeks; change from baseline cough severity after 12 weeks measured by the cough severity VAS; the percentage of participants with ≥30-scale unit reduction from baseline after 12 weeks measured by the cough severity VAS [22]; change from baseline cough-related QoL after 12 weeks measured by the LCQ; and the percentage of participants with ≥1.3-point increase from baseline after 12 weeks measured by LCQ total score [23].

Treatment-emergent AEs and serious AEs (SAEs) were recorded according to the Medical Dictionary for Regulatory Activities version 24.0. Additional safety assessments are described in the Supplementary Methods. At the study end, participants who spontaneously reported a taste-related AE completed an assessment on taste disturbances.

Statistical Analysis

A multiple comparison procedure modeling (MCP-Mod) approach [24] was used as the prespecified analysis of the primary efficacy endpoint. As PAGANINI was a phase 2b dose-finding study, the MCP-Mod approach was used because it is a well-accepted method for dose finding that efficiently uses the available data better than traditional pairwise

comparisons [25, 26]. The MCP-Mod approach enables the estimation of a dose response and the selection of an optimum dose for further phase 3 trials [26].

For the primary endpoint analysis, the raw 24-hour cough count was standardized to an average hourly count, then log-transformed as done previously [12, 27]. To detect a dose–response signal, four candidate dose–response models were tested with a single contrast test using the generalized MCP-Mod approach. The null hypothesis, “the response at all doses is equal,” was tested against the alternative, “there is a dose–response relationship.” If at least one of the four individual tests of models was statistically significant (adjusted *p* of one-sided test ≤0.1), a dose–response signal was considered established. The model with the best fit was then used for the estimation of the dose–response curve and the minimum effective dose (MED). For further information on the primary endpoint analysis, see the Supplementary Methods.

Sample size calculations were performed for establishing evidence of a drug effect across the doses. A sample size of 50 participants per dose group was predicted to have at least 85% power to demonstrate a dose–response relationship for the primary efficacy endpoint, using a one-sided test at a type I error rate of α=0.10 (see the Supplementary Methods for more details).

The secondary endpoint analyses and definitions of the per protocol, full analysis and safety analysis sets are described in the Supplementary Methods.

Statistical evaluation was performed using SAS software version 9.4 or higher (SAS Institute, USA) or ValidR software version 3.5.2 or higher (Mango Solutions, UK). Confirmatory *p*-values are reported for the analysis of the primary endpoint. The study was not powered for individual pairwise comparisons between dose groups. Analysis of secondary endpoints, sensitivity analyses, and AEs should be interpreted as exploratory.

Results

Of 399 participants screened between October 2, 2020 and March 12, 2021, 310 were randomized to eliapixant 25 mg (*n*=75), 75 mg (*n*=78), 150 mg (*n*=80), or placebo (*n*=77) (Fig. 1). All randomized participants were included in the full and safety analysis sets. A total of 283 participants were included in the per protocol set (eliapixant 25 mg *n*=67, 75 mg *n*=69, 150 mg *n*=73, placebo *n*=74). In total, 276 participants (89%) completed the treatment period.

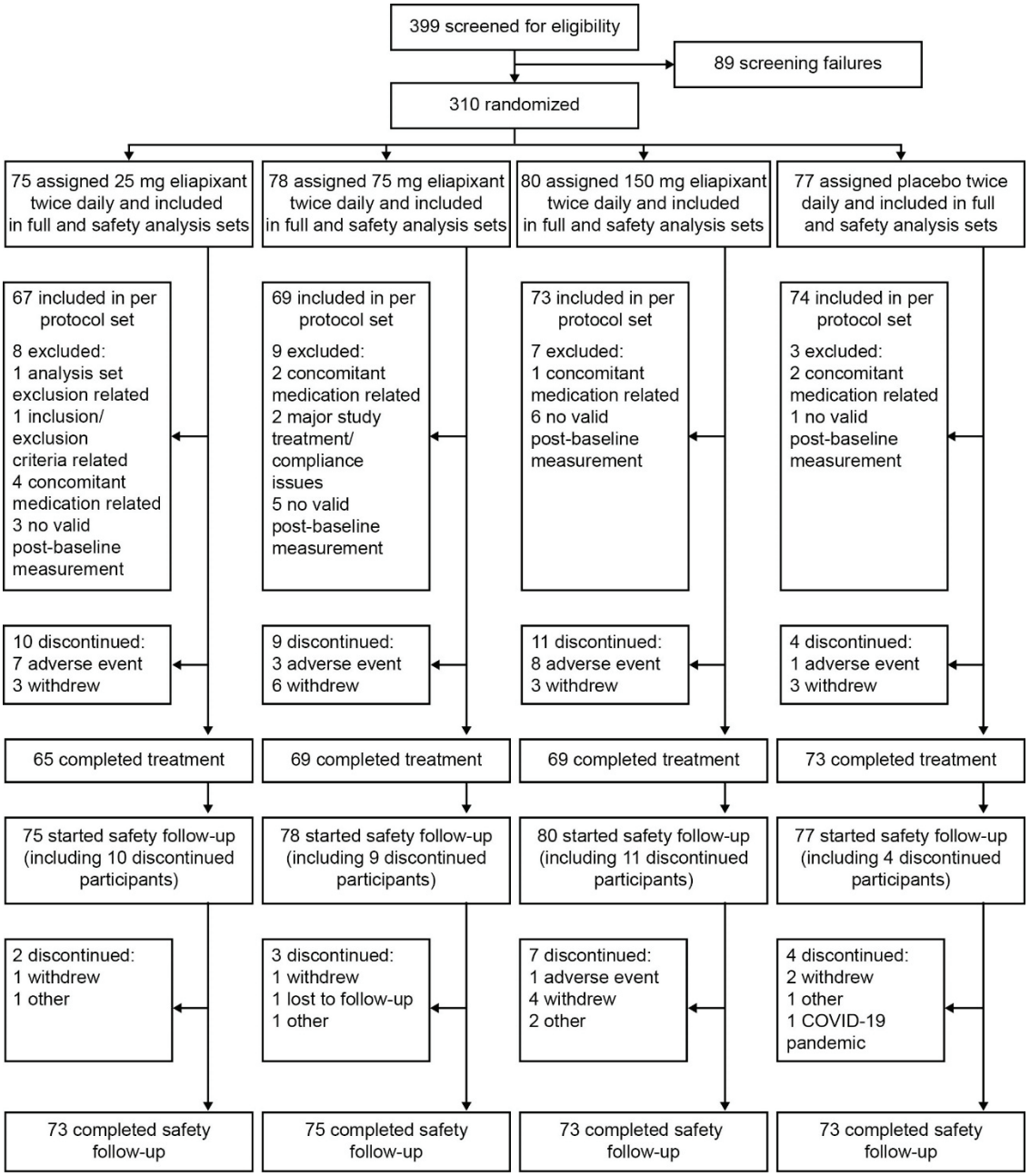

Fig. 1 Participant disposition. Includes the 12-week treatment period and the 30-day safety follow-up. If a participant has more than one validity finding that excludes them from an analysis set, all the findings are displayed. All 34 participants (11%) who discontinued the treatment phase of the study entered the safety follow-up. A total of 294 participants (95%) completed the 30-day safety follow-up. *COVID-19* corona virus disease 2019

Baseline demographics and clinical characteristics were generally well balanced across the treatment groups (Table 1), although mean 24-hour cough count (Table 2) and awake cough count in the eliapixant 150 mg group were slightly lower than in other groups. The baseline awake cough count was higher than the 24-hour cough count in all treatment groups. Overall, 76 (27%) participants had a low baseline 24-hour cough count of <10 coughs per hour.

Table 1 Baseline demographics and clinical characteristics (per protocol set)

Characteristics	Eliapixant 25 mg twice daily (*n*=67)	Eliapixant 75 mg twice daily (*n*=69)	Eliapixant 150 mg twice daily (*n*=73)	Placebo twice daily (*n*=74)
Age, years	61.2 (9.9)	59.1 (12.1)	59.3 (11.9)	56.6 (12.4)
≥65 years, *n* (%)	24 (36)	25 (36)	29 (40)	26 (35)
Female, *n* (%)	49 (73)	56 (81)	56 (77)	59 (80)
Race, *n* (%)				
White	56 (84)	60 (87)	66 (90)	64 (86)
Asian	10 (15)	9 (13)	5 (7)	10 (14)
Other/not reported	1 (1)	0	2 (3)	0
Geographic region, *n* (%)				
Europe	35 (52)	37 (54)	42 (58)	40 (54)
Japan	6 (9)	6 (9)	5 (7)	6 (8)
Rest of the world	26 (39)	26 (38)	26 (36)	28 (38)
Body mass index, kg/m^2	27.1 (4.7)	27.1 (5.5)	27.9 (5.7)	27.2 (5.1)
Duration of cough, years, *n* (%)				
<10	38 (57)	39 (57)	46 (63)	39 (53)
≥10	29 (43)	30 (43)	27 (37)	35 (47)
Tobacco smoking history, *n* (%)				
Never	47 (70)	51 (74)	48 (66)	56 (76)
Ex-smoker	20 (30)	18 (26)	25 (34)	18 (24)
Baseline 24-hour coughs, per hour[a]				
<10, *n* (%)	21 (31)	18 (26)	20 (27)	17 (23)
≥10, *n* (%)	46 (69)	51 (74)	53 (73)	57 (77)
≥20, *n* (%)	30 (45)	37 (54)	31 (42)	37 (50)
≥30, *n* (%)	21 (31)	23 (33)	15 (21)	24 (32)
Baseline awake coughs, per hour				
Geometric mean	23.6 (3.0)	26.4 (3.0)	21.2 (2.4)	24.0 (3.2)
<20, *n* (%)	28 (42)	26 (38)	30 (41)	32 (43)
≥20, *n* (%)	39 (58)	43 (62)	43 (59)	42 (57)
Baseline cough severity, VAS 0–100				
Arithmetic mean[b]	65.5 (14.6)	67.1 (14.9)	66.8 (15.9)	61.5 (18.5)
LCQ total score (range 3–21)				
Arithmetic mean	12.0 (2.5)	11.8 (2.8)	11.2 (2.6)	11.5 (3.3)

Data are expressed as mean (SD) unless otherwise stated

[a]See Table 2 for baseline geometric mean (SD) 24-hour coughs, per hour; [b]Eliapixant 25 mg twice daily *n*=62, eliapixant 75 mg twice daily *n*=68, eliapixant 150 mg twice daily *n*=67, placebo twice daily *n*=69

LCQ Leicester Cough Questionnaire, *SD* standard deviation, *VAS* visual analog scale

The data for the primary efficacy endpoint, change from baseline in 24-hour cough count after 12 weeks of intervention, are shown in Table 2 and Fig. 2A. At Week 12, the 24-hour cough count had decreased from baseline in all treatment groups. The largest relative and placebo-adjusted reductions in 24-hour cough count from baseline were seen in the 75 mg eliapixant group.

Table 2 Change from baseline in 24-hour cough count after 12 weeks of intervention (per protocol set)

	Eliapixant 25 mg twice daily (*n*=67)	**Eliapixant 75 mg twice daily (*n*=69)**	**Eliapixant 150 mg twice daily (*n*=73)**	**Placebo twice daily (*n*=74)**
Baseline geometric mean (SD) 24-hour coughs, per hour	17.5 (2.9)	19.2 (2.9)	15.6 (2.3)	17.6 (3.1)
Week 12 geometric mean (SD) 24-hour coughs, per hour	9.0 (4.0)	9.1 (3.8)	8.1 (2.7)	11.3 (3.1)
Relative change of geometric means for 24-hour cough at Week 12, % (95% CI)	–44 (–55 to –29)	–53 (–62 to –42)	–48 (–57 to –36)	–36 (–47 to –23)
Change in 24-hour cough count at Week 12 relative to placebo, % (95% CI)	–12 (–30 to 11)	–27 (–41 to –9)	–18 (–33 to <1)	—

CI confidence interval, *SD* standard deviation

For the primary analysis of the primary endpoint, a statistically significant dose–response signal was detected with eliapixant for change from baseline in 24-hour cough

count at Week 12, with multiplicity-adjusted *p*-values of <0.1 for all four candidate models (Supplementary Table S1). As a result of the better model fit, the Emax model was used to derive the MED (Fig. 2B). The MED to achieve a relative change vs. placebo of –20% (i.e., log[0.8] = –0.22 on the log-transformed scale [Fig. 2B]) was estimated at ~58 mg eliapixant twice daily.

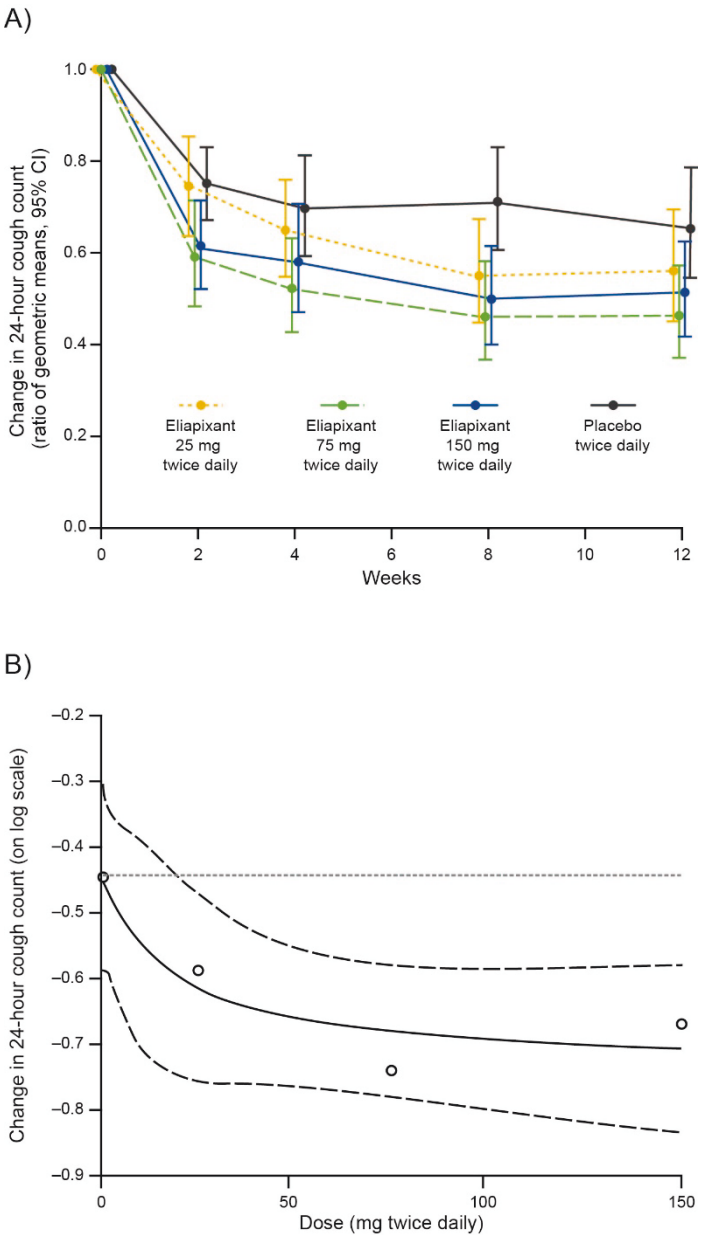

Fig. 2 (**A**) Change from baseline in 24-hour cough count throughout study period and (**B**) the estimated dose–response Emax model for the change from baseline to Week 12 in log-transformed 24-hour cough count with an 80% CI (per protocol set). In (**B**), circles indicate the estimated dose response in each dose group adjusted for baseline cough count and

geographic region. The dotted horizontal reference line at –0.44 represents the estimated dose response in the placebo group. The solid line indicates the estimated Emax dose–response model and the dashed lines indicate the 80% CI.
CI confidence interval, *Emax* asymptotic maximum change from placebo effect

Reductions in 24-hour cough count with the two higher doses of eliapixant relative to placebo were observed early at Week 2, with further reductions at Week 4 and Week 8 (Fig. 2A). A ≥30% reduction from baseline in 24-hour cough count at Week 12 was reported in 34 participants (46%) with placebo and 35–44 participants (52–64%) receiving eliapixant. Compared with placebo, more participants in the 75 mg group reached this responder threshold at Week 12 (mean treatment difference: 18%, 95% confidence interval [CI] 2 to 34, p=0.03). A smaller treatment difference vs. placebo was observed for the other doses of eliapixant with a mean treatment difference of 6% (95% CI –10 to 23, p=0.5) and 8% (95% CI –9 to 24, p=0.4) for the 25 mg and 150 mg groups, respectively.

Similar findings to those for 24-hour cough count were observed for the change from baseline in awake cough count at all study visits (see Supplementary Results and Supplementary Fig. S2 for more details).

Cough severity was reduced with all doses of eliapixant at Week 12 vs. baseline, with a small numeric reduction vs. placebo (Table 3). More participants in the 75 mg group experienced a ≥30-scale unit reduction in cough severity at Week 12 vs. placebo (mean treatment difference of 16%, 95% CI 1 to 31, p=0.03). A smaller treatment difference vs. placebo was observed for the other doses of eliapixant (Table 3).

Table 3 Secondary efficacy cough-related endpoints relating to severity and QoL (per protocol set)

	Eliapixant 25 mg twice daily (*n*=67)	**Eliapixant 75 mg twice daily (*n*=69)**	**Eliapixant 150 mg twice daily (*n*=73)**	**Placebo twice daily (*n*=74)**
Cough severity[a]				
Mean (SD) change in cough severity from baseline to Week 12	–17.7 (23.8)	–22.7 (23.0)	–22.9 (24.5)	–17.0 (21.9)
LS mean (SE) change in cough severity from baseline to Week 12[b]	–19.0 (3.1) *p*<0.0001	–23.3 (2.9) *p*<0.0001	–23.5 (3.0) *p*<0.0001	–18.0 (2.7) *p*<0.0001
Treatment difference vs. placebo, difference of LS means (SE)[b]	–0.9 (4.0) *p*=0.8	–5.3 (3.8) *p*=0.2	–5.4 (4.0) *p*=0.2	
Participants with a ≥30-scale unit reduction in cough severity from baseline to Week 12, *n* (%)	18 (27)	25 (36)	20 (27)	15 (20)
Treatment difference vs. placebo, % (SE)	7 (0.1) *p*=0.4	16 (0.1) *p*=0.03	7 (0.1) *p*=0.3	
Cough-related QoL[c]				
Mean (SD) change in LCQ total score from baseline to Week 12	2.2 (3.4)	2.5 (3.3)	2.7 (3.5)	2.2 (3.1)
LS mean (SE) change in LCQ total score from baseline to Week 12[b]	2.2 (0.4) *p*<0.0001	2.5 (0.4) *p*<0.0001	2.6 (0.4) *p*<0.0001	2.1 (0.4) *p*<0.0001
Treatment difference vs. placebo, difference of LS means (SE)[b]	0.1 (0.6) *p*=0.9	0.4 (0.5) *p*=0.5	0.5 (0.5) *p*=0.4	
Participants with a ≥1.3-point increase in LCQ total score from baseline to Week 12, n (%)	32 (48)	42 (61)	47 (64)	38 (51)
Treatment difference vs. placebo, % (SE)	–4 (0.1) *p*=0.7	10 (0.1) *p*=0.3	13 (0.1) *p*=0.1	

[a]Measured by the cough severity visual analog scale; [b]A mixed model repeated measures analysis was applied with baseline value, treatment group, region, visit, and treatment by visit interaction as fixed effects, and participant as a random effect using an unstructured covariance structure; [c]Measured by LCQ total score

LCQ Leicester Cough Questionnaire, *LS* least squares, *QoL* quality of life, *SD* standard deviation, *SE* standard error

There was a dose-dependent improvement in LCQ total score after 12 weeks. However, the differences vs. placebo were small (0.1, 95% CI –1.0 to 1.2, in the 25 mg group; 0.4, 95% CI –0.7 to 1.4, in the 75 mg group; 0.5, 95% CI –0.6 to 1.6 in the 150 mg group) (Table 3). The percentage of participants with a ≥1.3-point increase in LCQ total score from baseline after 12 weeks was similar between all three doses of eliapixant and placebo.

Sensitivity analyses of the full analysis set confirmed the primary endpoint and secondary endpoint results in the per protocol set (data not shown).

AEs were reported in 39 participants (51%) with placebo and 43–51 participants (57–65%) receiving eliapixant, with most considered mild or moderate (Table 4). The proportion of participants reporting AEs (including those described as severe) was slightly higher in the two higher-dose eliapixant groups than the low-dose eliapixant or placebo groups (Table 4). The most frequently occurring AE was dysgeusia, which occurred in 1 participant (1%) in the placebo group and 1–13 participants (1–16%) in the eliapixant group in a dose-related manner (Table 5). Other AEs relating to taste or smell disorders were similarly more frequent with eliapixant than placebo (Table 5).

Table 4 Summary of treatment-emergent AEs (safety analysis set)

Patients, *n* (%)	Eliapixant 25 mg twice daily (*n*=75)	Eliapixant 75 mg twice daily (*n*=78)	Eliapixant 150 mg twice daily (*n*=80)	Placebo twice daily (*n*=77)
Any AE	43 (57)	51 (65)	51 (64)	39 (51)
Maximum intensity for any AE				
Mild	21 (28)	31 (40)	23 (29)	18 (23)
Moderate	22 (29)	16 (21)	25 (31)	20 (26)
Severe	0	3 (4)	3 (4)	1 (1)
Any study drug-related AE	9 (12)	15 (19)	30 (38)	9 (12)
Maximum intensity for study drug-related AE				
Mild	5 (7)	10 (13)	16 (20)	7 (9)
Moderate	4 (5)	5 (6)	12 (15)	2 (3)
Severe	0	0	2 (3)	0
AEs leading to study drug discontinuation	7[a] (9)	3[b] (4)	8[c] (10)	1[d] (1)
Any SAE	0	1 (1)	2 (3)	1 (1)
Any study drug-related SAE	0	0	1 (1)	0
SAEs leading to study drug discontinuation	0	0	1 (1)	1 (1)
AEs with outcome death	0	0	0	0

Treatment-emergent AEs are reported from the start of study intervention administration until 14 days after the last study medication intake

[a]*n*=1 each for cough, arthralgia, abdominal pain upper, dizziness, diplopia/pain in extremity/headache, musculoskeletal chest pain, or gastroenteritis; [b]*n*=1 each for pancytopenia, asthenia/chest discomfort/hypotension, or palpitations/diarrhea/fatigue/disturbance in attention; [c]*n*=1 each for liver function test abnormal, throat irritations, nausea/chills/fatigue/weight increased, dizziness/dysgeusia/headaches/asthma/hemoptysis, cough, alanine aminotransferase increased/aspartate aminotransferase increased, abdominal pain upper, rash, or arthralgia/pain in extremity; [d]*n*=1 for angina unstable

AE adverse event, *SAE* serious adverse event

AEs leading to study drug discontinuation were more common with eliapixant than placebo (Table 4). An SAE of abnormal liver tests leading to study drug discontinuation occurred in 1 participant in the 150 mg eliapixant group and was reported as a suspected unexpected serious adverse reaction (SUSAR). No deaths occurred during the study.

Table 5 Most frequently reported treatment-emergent AEs, and AEs related to taste, bleeding, and drug-related hepatic disorders (safety analysis set)

Patients, *n* (%)	**Eliapixant 25 mg twice daily (*n*=75)**	**Eliapixant 75 mg twice daily (*n*=78)**	**Eliapixant 150 mg twice daily (*n*=80)**	**Placebo twice daily (*n*=77)**
Most frequently reported AEs[a]				
Dysgeusia	1 (1)	9 (12)	13 (16)	1 (1)
Headache	6 (8)	5 (6)	6 (8)	4 (5)
Cough	4 (5)	7 (9)	7 (9)	3 (4)
Fatigue	2 (3)	6 (8)	5 (6)	2 (3)
Dry mouth	1 (1)	3 (4)	2 (3)	4 (5)
Dizziness	2 (3)	2 (3)	1 (1)	5 (6)
Nausea	2 (3)	2 (3)	5 (6)	1 (1)
Hypogeusia	2 (3)	1 (1)	4 (5)	2 (3)
Insomnia	4 (5)	0	1 (1)	0
Taste-related AEs				
Dysgeusia	1 (1)	9 (12)	13 (16)	1 (1)
Hypogeusia	2 (3)	1 (1)	4 (5)	2 (3)
Taste disorder	0	2 (3)	1 (1)	1 (1)
Ageusia	0	0	2 (3)	1 (1)
Any AE relating to “taste and smell disorders”[b]	3 (4)	12 (15)	19 (24)	5 (6)
Any AE relating to “hemorrhages”[b]	3 (4)	2 (3)	5 (6)	2 (3)
Any AE relating to “drug-related hepatic disorders – comprehensive search”[b]	0	1 (1)	3 (4)	0

Treatment-emergent AEs are reported from the start of study intervention administration until 14 days after the last study medication intake

[a]AEs reported in ≥5% in any treatment group; [b]Identified via standardized Medical Dictionary for Regulatory Activities query

AE adverse event, *SAE* serious adverse event

Changes in some laboratory safety parameters were reported, including 2 participants receiving eliapixant (75 mg, *n*=1; 150 mg, *n*=1) who had alanine aminotransferase exceeding the three-fold upper limit of normal, which triggered close liver observation in accordance with the US Food and Drug Administration Guidance for Industry [28] and the study protocol. In the patient receiving eliapixant 150 mg, the SUSAR was considered a moderate drug-induced liver injury (DILI) of hepatocellular origin. The participant prematurely discontinued eliapixant at the 4-week visit because of the liver event, after which the liver enzyme values returned to normal. In the overall population, dose-dependent increases in mean and median values of alkaline phosphatase, fibrinogen, and plasma antithrombin III activity were observed. There were no relevant mean changes in other liver enzymes at any dose of eliapixant during treatment in the overall population. See the Supplementary Results for more details.

Thirty-one participants who spontaneously reported a taste-related AE during the treatment period completed an end-of-study assessment on taste disturbances (Fig. 3). The frequency and how bothersome the taste disturbances were in the eliapixant groups increased in a dose-related manner (Fig. 3A). No participants described the taste effects as “extremely” bothersome. An answer of “very” bothersome was only recorded in the 150 mg group (Fig. 3B).

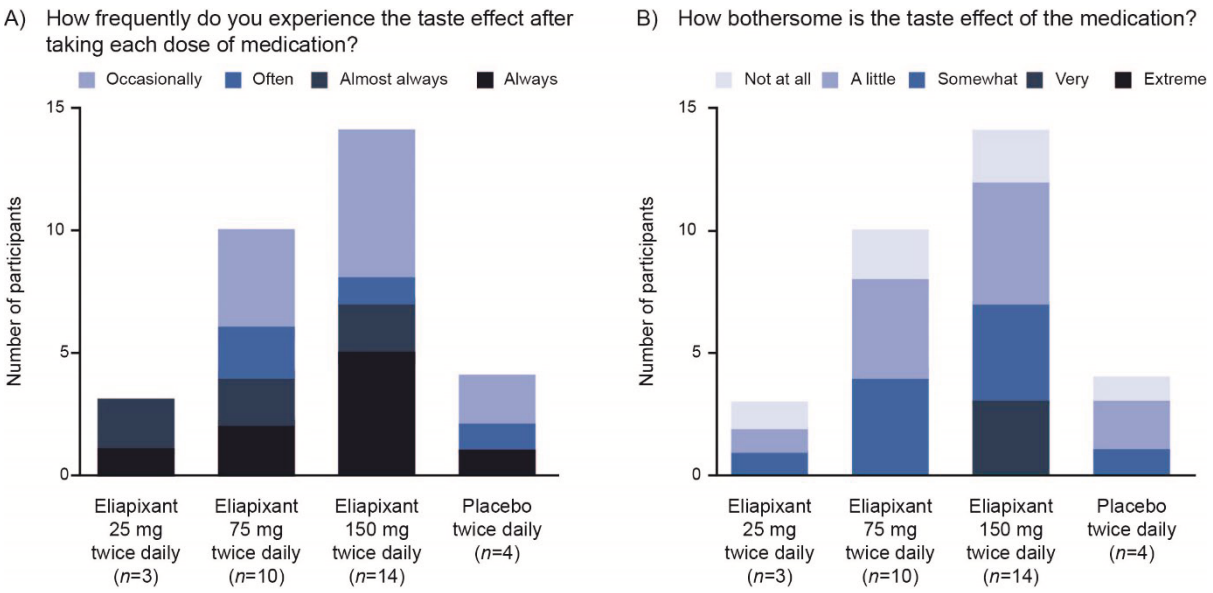

Fig. 3 End-of-study assessment on taste disturbances (safety analysis set)[a]. [a]*n*=31 patients who spontaneously reported a taste-related AE and completed the taste questionnaire

Discussion

PAGANINI confirmed data from the phase 2a study suggesting that eliapixant is effective at reducing 24-hour cough count in patients with RCC. The detection of a statistically significant dose–response signal with eliapixant was achieved for the primary endpoint of change from baseline in 24-hour cough count at Week 12. At Week 12, 24-hour cough count was reduced by 27% vs. placebo in the 75 mg group. In an analysis of secondary efficacy endpoints, awake cough count was also reduced by 28% with 75 mg eliapixant vs. placebo at Week 12. Compared with placebo, more participants in the 75 mg eliapixant group reached a ≥30% reduction in 24-hour cough count and ≥30-scale unit reduction in cough severity at Week 12 from baseline; however, cough-related QoL as measured by LCQ total score did not improve.

The phase 2a study of eliapixant demonstrated similar reductions in 24-hour cough and awake cough counts to those reported here [18]. However, the improvements in cough severity and cough-related QoL vs. placebo seen in the earlier study [18] were not observed to the same extent. While comparisons between studies should be made with caution, this

observation may be explained by the larger placebo response seen in PAGANINI. However, improvements in cough severity and cough-related QoL were reported for the phase 2b gefapixant and sivopixant trials [12, 27], and the phase 3 COUGH-1 and COUGH-2 studies despite large placebo effects [13]. The lack of patient-perceived improvement in cough in this study is therefore difficult to explain. However, it should be noted that PAGANINI was not powered to detect significant differences in patient-reported outcome parameters between treatment groups.

In this study, the efficacy effects in the 150 mg eliapixant group were not greater than those in the 75 mg group, suggesting that a plateau in dose response was reached, as indicated by the estimated dose–response curve. This finding may have also been influenced by the less severe baseline cough characteristics in the 150 mg group. A plateau in dose response for reduction in cough count was also observed with eliapixant in the phase 2a study, although subjective endpoints continued to improve with the highest dose [18]. The plateau in dose response is also supported by data from healthy volunteers [16], whereby the two higher doses of eliapixant had similar trough plasma drug concentrations, and the plasma concentrations predicted to achieve ≥80% P2X3 receptor occupancy (the expected threshold for efficacy based on unpublished preclinical studies; data on file, Bayer AG) were reached with both higher doses [16]. Achievement of the primary endpoint and the low MED to achieve 20% improvement over placebo are therefore notable considering the globally heterogeneous study population, the high placebo response, the overall high number of participants experiencing a low baseline 24-hour cough count of <10 coughs per hour, and the lower baseline cough counts and efficacy results in the 150 mg eliapixant group.

The safety and tolerability profiles in PAGANINI are generally consistent with other studies of eliapixant in healthy subjects and the phase 2a study in patients with RCC [16–18]. However, a case of a moderate DILI of hepatocellular origin occurred during treatment with 150 mg eliapixant and contributed to the need for intensified liver monitoring in clinical trials with eliapixant. In a second participant, alanine aminotransferase levels exceeding the

three-fold upper limit of normal led to close liver observation, and a dose-dependent increase in mean alkaline phosphatase levels in the overall population was observed during the treatment period. The clinical relevance of increased alkaline phosphatase levels is unclear, as is the origin (liver vs. bone) in the absence of a concurrent increase in the mean values of other liver enzymes. In the phase 2a study of the P2X3 antagonist sivopixant for RCC, a participant receiving sivopixant also experienced a DILI during the trial [29].

Taste-related AEs were reported in 24% of participants in the 150 mg eliapixant group with fewer reports in participants receiving lower doses. One participant discontinued treatment due to dysgeusia as part of a combination of nine AEs. No participants who spontaneously reported a taste-related AE described the effect as “extremely” bothersome. As with the phase 2b study of gefapixant [12], dysgeusia was the most reported AE in PAGANINI. However, taste-related AEs were previously reported in up to 81% of patients with gefapixant in phase 2b [12] compared with up to 24% of participants with eliapixant in this study. In phase 3 trials with gefapixant 45 mg, taste-related AEs were reported by 59% of participants at Week 12 in COUGH-1 and 69% of participants at Week 24 in COUGH-2 [13]. The smaller impact on taste perception with eliapixant may be due to its high selectivity for the P2X3 receptor leading to a low potential for off-target effects mediated by P2X2/3 receptors [16].

Strengths of PAGANINI included that the baseline demographics reflect those seen in the clinical RCC population [30]. Recruitment of participants across 19 countries means the results are likely to reflect the global population of patients with RCC. Limitations of the study include a lack of powered individual pairwise comparisons between dose groups; however, the aim of this study was to establish evidence of a drug effect across the doses to support the dose selection for phase 3 studies [25, 26].

In summary, the PAGANINI study showed that eliapixant was effective at reducing 24-hour cough count vs. placebo in patients with RCC. The safety and tolerability profiles in PAGANINI were consistent with other studies of eliapixant in healthy subjects and the phase 2a study in patients with RCC. However, a case of a moderate DILI of hepatocellular origin

occurred during treatment with 150 mg eliapixant. This DILI contributed to the need for intensified liver monitoring in clinical trials with eliapixant and the subsequent discontinuation of the entire development program in all indications by Bayer AG.

Funding Bayer AG funded the PAGANINI study.

Author Contributions KG, UK, RS, PVP, and MW designed the study. AHM, MRS, MV, LMG, and AN collected data. All authors interpreted the data. UK undertook statistical analyses. All authors critically reviewed and revised the manuscript and approved the final version for publication.

Conflict of Interest PVD reports remuneration for consultancy from Bayer AG, Bellus Health, Chiesi, Merck, and Shionogi. AHM reports remuneration for consultancy from Bayer AG, Bellus Health, Boehringer Ingelheim, Merck, Pfizer, Procter & Gamble, and Shionogi, lecture fees from AstraZeneca and Boehringer Ingelheim, and grant support from Afferent Pharmaceuticals, Infirst, Merck, and Procter & Gamble. JAS reports research grants and remuneration for consultancy from Algernon, AstraZeneca, Axalbion, Bayer AG, Bellus Health, Boehringer Ingelheim, Chiesi, Merck, Nocion Therapeutics, Shionogi, and Trevi, and non-financial support and royalties from Vitalograph paid to Manchester University NHS Foundation Trust that may be shared with the department in which JAS works. JAS is funded by the Manchester NIHR Biomedical Research Centre and an NIHR Senior Investigator Award. MRS reports research grants from Afferent Pharmaceuticals, Bayer AG, Bellus Health, Merck, NeRRe Therapeutics, and Shionogi, remuneration for lectures from Merck, and has served on advisory committees for Afferent Pharmaceuticals, AstraZeneca, Bayer AG, Bellus Health, Merck, NeRRe Therapeutics, Nocion Therapeutics, and Shionogi and on a Data and Safety Monitoring Board for Nocion Therapeutics. MV reports remuneration for consultancy in litigation relating to acid suppressive therapy, has served on an advisory committee for Bayer AG, Diversatek, Ironwood, ISOThrive, Medtronic, Phathom, and Sanofi, and holds a patent with Diversatek. LG reports a research grant from AstraZeneca, remuneration for lectures from AstraZeneca, Bayer AG, GlaxoSmithKline, MSD, Novartis, and Sanofi, and remuneration for consultancy from AstraZeneca, Bayer AG, Chiesi, GlaxoSmithKline, Merck, MSD, Novartis, and Sanofi. AN reports research grants

from Kyorin Pharmaceutical and Novartis and remuneration for lectures from AstraZeneca, GlaxoSmithKline, Kyorin Pharmaceutical, MSD, and Novartis. KG, UK, RS, and MW are employees of Bayer AG. PVP was an employee of Bayer AG at the time of the study and is now an employee of the Janssen Pharmaceutical Companies of Johnson & Johnson. LMG reports research grants from Bayer AG, Bellus Health, Chiesi, Merck, and Shionogi, remuneration for lectures from Bayer AG, Bellus Health, Chiesi, GlaxoSmithKline, Merck, and Shionogi, remuneration for consultancy from Bayer AG, Bellus Health, Chiesi, Merck, NeRRe Therapeutics, Nocion Therapeutics, and Shionogi, and has served on advisory committees for Applied Clinical Intelligence, Bayer AG, Bellus Health, Chiesi, Merck, NeRRe Therapeutics, Nocion Therapeutics, and Shionogi and on a Data and Safety Monitoring Board for Bayer AG.

Data Sharing 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, timepoint, 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 January 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized 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 anonymized patient-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the

decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

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Supplementary Material

Efficacy and Safety of Eliapixant in Refractory Chronic Cough: The Randomized, Placebo-Controlled Phase 2b PAGANINI Study

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Supplementary Methods

Participating Regions and Countries

The following regions and countries participated in PAGANINI and enrolled participants: Europe (Belgium, Czech Republic, France, Germany, Hungary, Italy, the Netherlands, Poland, Slovakia, Spain, and the United Kingdom), Japan, and the rest of the world (Argentina, Australia, Canada, the Russian Federation, Taiwan, Turkey, and the United States of America).

Full Inclusion Criteria

1. Adults ≥18 years of age at the time of signing the informed consent.
2. A cough that has lasted for ≥12 months with persistently bothersome refractory (unresponsive to treatment options) or idiopathic (unexplained) chronic cough that has lasted for ≥8 weeks before screening.
3. Cough severity as measured by visual analog scale ≥40 units at screening.
4. Women of childbearing potential must agree to use acceptable effective or highly effective birth control methods (as per Clinical Trials Facilitation and Coordination Group guidelines) during the study and for ≥30 days after the last dose.
5. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form and the study protocol.

Full Exclusion Criteria

Refractory Chronic Cough (RCC)-Related Medical Conditions

1. Smoking history within the last 12 months before screening (all forms of smoking, including e-cigarettes, cannabis, and others), and any former smoker with >20 pack-years.

2. Ongoing or previous exposure to inhalational toxic fumes (e.g., ammonia, chlorine, nitrogen dioxide, phosgene, and sulfur dioxide) within the last 12 months before screening.
3. Chest radiograph or computerized tomography scan within the last 24 months before screening and subsequent to the onset of chronic cough with presence of any obvious lung disease that could be responsible for or contributing to the cough (e.g., bronchiectasis, cavitary lesions, interstitial pulmonary fibrosis, pneumothorax, pleural disease, unstable rib fracture, and tuberculosis).
4. Forced expiratory volume in 1 second/forced vital capacity ratio <60% or a history of frequent exacerbations of chronic obstructive pulmonary disease.
5. Respiratory tract infection within 4 weeks before screening.
6. History of chronic bronchitis.
7. Active state of massive hemoptysis[a] or pulmonary hemorrhage, including those events managed by bronchial artery embolization or any history of bronchial artery embolization or massive hemoptysis within 3 months prior to screening.

Hepatic-Related Criteria

8. Moderate-to-severe hepatic impairment defined as Child–Pugh Class B or C.
9. Alanine aminotransaminase >2 × the upper limit of normal (ULN), or aspartate aminotransaminase >2 × ULN, or total bilirubin greater than the ULN, or alkaline phosphatase >2 × ULN, or international normalized ratio greater than the ULN (unless related to anticoagulation treatment).

Renal-Related Criteria

10. Estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease formula. Different eGFR formula were used for participants enrolled at sites in Japan[b].

General Medical Conditions

11. Uncontrolled hypertension despite optimal treatment with antihypertensive(s), indicated by a sitting systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg.
12. Any other diseases or conditions that according to the investigator can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study intervention (e.g., chronic bowel disease, Crohn's disease, and ulcerative colitis).
13. Esophageal achalasia.
14. Any serious or unstable diseases or conditions including psychiatric disorders that might interfere with the conduct of the study or the interpretation of the results.
15. Concurrent malignancy or history of cancer (exception of basal cell or squamous cell carcinoma of the skin) within the last 5 years prior to screening.

Prior/Concomitant Therapy

16. Intention to start new treatment for RCC during the study.
17. Intake of prohibited prior or concomitant therapy. A list of prohibited prior and concomitant medications, along with the time frame, is provided in Supplementary Table S2. Medications that are allowed only if the participant is on stable treatment (prior to and at enrollment) are shown in Supplementary Table S3.

Other Exclusions

18. Body mass index >40 kg/m^2.
19. Hypersensitivity to any ingredient of the study intervention.
20. Wish for pregnancy during the study, current pregnancy, or lactation.
21. Major surgery scheduled during the study period.
22. Inability to cooperate with the study procedures for any reason, including the following examples: language comprehension and inability to get to the study site.
23. Abuse of alcohol or medicines or use of recreational/illicit drugs, as evaluated by the investigator.
24. Previous assignment to treatment (e.g., randomization) during this study.

25. Simultaneous participation in another clinical trial with investigational medicinal product(s).
26. Participation in another P2X3 trial within 3 months prior to screening.
27. Close affiliation with the investigational site, e.g., a close relative of the investigator, dependent person (e.g., employee or student of investigational site, or sponsor's staff).
28. Otherwise vulnerable participants. Participants who are in custody by order of an authority or a court of law.

[a]Massive hemoptysis is a medical emergency defined as any degree of hemoptysis causing life-threatening clinical consequences such as, but not limited to, respiratory failure from airway obstruction, hypoxemia requiring mechanical ventilation, transfusion, and hypotension [1].

[b]In Japan, the equation recommended by the Japanese Society of Nephrology [2] was used for participants enrolled at Japanese sites in this study

(for men: eGFRcreat [mL/min/1.73m^2] = 194 × Cr$^{-1.094}$ × age$^{-0.287}$,

for women: eGFRcreat [mL/min/1.73m^2] = 194 × Cr$^{-1.094}$ × age$^{-0.287}$ × 0.739).

Additional Information on Procedures

Cough Count Measurements

Cough monitoring with the ambulatory cough recording device recorder (VitaloJAK, Vitalograph Ireland, Ltd) was started at approximately the same time of day on each of the assessment days. On approximately 98% of analyzed recordings, an algorithm (VitaloJAK, Vitalograph Ireland, Ltd) was used to remove background noise and to compress the recording. Cough sounds were counted using an audio editing package (VitaloJAK, Vitalograph Ireland, Ltd).

Cough count measurements were considered invalid for the primary analysis if the duration of recording was <20 hours. If the treatment compliance between the previous visit and the visit of the cough count measurement was <80% or >120%, the measurement was also considered invalid for the primary analysis. The minimum required treatment duration was up to and including Week 2 to allow for a valid post-baseline cough count measurement.

Electronic Patient-Reported Outcomes (PROs)

Participants completed the cough severity visual analog scale (VAS) using an electronic PRO handheld device and the Leicester Cough Questionnaire (LCQ) using a tablet device. All PRO questionnaires were provided in the participant's local language and completed by the study participants. Following standardized technical training on the use of the handheld device and the tablet device during screening, the participants confirmed their understanding of the use of the devices and the completion of the PROs. Alarms on the electronic handheld devices were set to remind the study participants to complete the PROs at the same time every day.

Additional Information on Safety-Related Assessments

In addition to the recording of adverse events throughout the study, the following safety assessments were performed:

- A comprehensive physical examination was performed by the investigator at screening, baseline, and Week 12.
- Vital signs (blood pressure and heart rate) were assessed at all site visits.
- Twelve-lead electrocardiograms were performed at screening, Week 12, and the safety follow-up.
- Spirometry was conducted at screening in accordance with guidelines from the American Thoracic Society and European Respiratory Society Task Force. Available

lung function testing results were considered as baseline if they were not older than 3 months prior to screening.

The following laboratory parameters were assessed at screening, Week 4, Week 8, Week 12, and follow-up:

- Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes, and platelets.
- Blood chemistry: sodium, potassium, calcium, magnesium, phosphorus, creatinine, cystatin C, total protein, albumin, and eGFR.
- Liver enzymes[a]: alkaline phosphatase, γ-glutamyl transferase, alanine aminotransferase, aspartate aminotransferase, and total bilirubin.
- Carbohydrate metabolism: serum glucose and hemoglobin-A1C.
- Lipid tests: total cholesterol, triglyceride, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol.
- Coagulation tests: prothrombin time, activated partial thromboplastin time, fibrinogen, international normalized ratio, and antithrombin III.
- Pancreas tests: pancreatic α-amylase and lipase.

Pregnancy testing was completed for women of childbearing potential only. A serum test was conducted at screening, otherwise urine pregnancy tests were used every 4 weeks from baseline until the safety follow-up.

[a]An increase in liver function parameters was regarded as a potential risk based on animal data (data not shown) and therefore liver function parameters were monitored throughout the study.

Additional Information on Statistical Analysis

Sample Size Calculations

The sample size calculation assumed a true change in 24-hour cough count during placebo treatment after 12 weeks of –0.19 (17% reduction), a maximum cough count change of –0.35 for eliapixant vs. placebo (30% reduction relative to placebo), a common standard deviation of 0.8 on the log scale (derived from phase 2a data of eliapixant in patients with RCC [5] and a literature review of other clinical studies in patients with RCC), and a set of dose–response shapes including two asymptotic maximum change from placebo effect (Emax) and two sigmoidal Emax models.

Primary Endpoint Analysis

The multiple comparison procedure modeling (MCP-Mod) method [3], combining multiple comparison procedure principles with modeling techniques, was used for primary analysis of the primary efficacy endpoint. This method allows flexibility of modeling for dose estimation, while preserving the robustness to model misspecification associated with MCP procedures. More specifically, a generalization of the original MCP-Mod method was used which allows dose–response testing and modeling in conjunction with the response variable being described by a parametric model [4]. The generalized MCP-Mod approach (i.e., adjusted for baseline cough count [to account for potential baseline imbalances] and geographic region [for administrative purposes and to account for ethnic and etiologic differences]) takes multiplicity into account [3, 4].

For MCP-Mod, the four candidate models were: an Emax model with parameters ED_{50}=30, an Emax model with parameter ED_{50}=50, a sigmoidal model with parameters ED_{50}=30 and Hill coefficient=3, and a sigmoidal model with parameters ED_{50}=60 and Hill coefficient=5. All these candidate models assumed a monotonically decreasing dose response. All parameters of the models are shown in Supplementary Fig. S3A and were based on phase 2a data of eliapixant in patients with RCC [5] and a literature review of other

clinical studies in patients with RCC. The dose–response relationships of the candidate models are shown in Supplementary Fig. S3B.

The estimand of interest to assess the detection of a trend in the dose relationship for the primary efficacy endpoint was the effect of the intervention in those participants who tolerated the intervention, adhered to the intervention schedule, and followed all current relevant protocol procedures. The attributes of the estimand were population (as described by the inclusion and exclusion criteria), variable (i.e., change from baseline in 24-hour cough count after 12 weeks of intervention), treatment (eliapixant or placebo), intercurrent events ("early discontinuation of study intervention," "non-compliance with study intervention," and "infection by COVID-19"), and population-level summary (estimated mean of change from baseline in the logarithm of average hourly cough count by intervention group). The intercurrent events considered most important were handled with the while-on-treatment strategy.

Secondary Endpoint Analyses

The relative change of geometric means for 24-hour cough count and awake cough count at Week 12 was calculated as the difference between geometric mean at Week 12 and at baseline, divided by the geometric mean at baseline. For the cough severity VAS and LCQ, the change from baseline was analyzed by means of a mixed model for repeated measurements with baseline value, treatment group, region, visit, and treatment by visit interaction as fixed effects, and participants as a random effect. An unstructured covariance structure with grouping by treatment group was fitted. The proportions of participants meeting the cough count, cough severity VAS, and LCQ responder thresholds were compared across intervention groups using a Chi-square test. Reported *p*-values for secondary endpoints are two-sided and are not adjusted for multiple testing.

Analyses Conducted Using Per Protocol Set, Full Analysis Set, or Safety Analysis Set

All efficacy endpoints were analyzed using the per protocol set, defined as all participants randomly assigned to study intervention who had no validity findings affecting efficacy. Sensitivity analyses of the primary and secondary endpoints were performed using the full

analysis set, defined as all participants randomly assigned to study intervention. Safety endpoints were analyzed in the safety analysis set, defined as all participants randomly assigned to study intervention who took ≥1 dose.

Supplementary Results

Awake Cough Counts at Week 12

At Week 12, the relative change of geometric means for awake cough count was –44% (95% CI –56 to –29) with eliapixant 25 mg, –53% (95% CI –63 to –42) with eliapixant 75 mg, –53% (95% CI –64 to –38) with eliapixant 150 mg, and –35% (95% CI –46 to –22) with placebo (Fig. 3). Relative to placebo, the change in awake cough count at Week 12 was –14% (95% CI –32 to 10), –28% (95% CI –42 to –11), and –27% (95% CI –44 to –5) in the eliapixant 25, 75, and 150 mg groups, respectively.

Changes in Laboratory Safety Parameters

Two participants receiving eliapixant had alanine aminotransferase (ALT) exceeding the three-fold ULN, which triggered close liver observation in accordance with the US Food and Drug Administration Guidance for Industry [6] and the study protocol:

- A serious adverse event of abnormal liver tests was reported by 1 participant (1%) in the 150 mg eliapixant group as a suspected unexpected serious adverse reaction and was considered related to the study drug and led to its discontinuation. The suspected unexpected serious adverse reaction was assessed by an external expert as a moderate drug-induced liver injury (DILI) of hepatocellular pattern. Due to nausea and vomiting, eliapixant treatment (150 mg twice daily) was interrupted at Week 2 by the participant before being reintroduced shortly before Week 4, when an almost 20-fold increase of ALT above the ULN was detected. Total bilirubin did not exceed the two-fold ULN. The participant prematurely discontinued eliapixant at the 4-week visit because of the liver event, after which the liver enzyme values returned to normal. The participant completed the 4-week safety follow-up following discontinuation.
- In the second close liver observation case, elevated ALT levels (>3 × ULN) did not meet the biochemical criteria for liver injury according to the criteria of the DILI Expert

Working Group [7]. The participant recovered and the liver enzyme values declined while the participant was still receiving 75 mg eliapixant.

Despite these two cases, there were no relevant changes in ALT, aspartate aminotransferase, bilirubin, or γ-glutamyl transferase at any dose of eliapixant during treatment in the overall population. However, a dose-dependent increase of the mean and median values of alkaline phosphatase was seen first at Week 4 after start of study intervention, and the values remained relatively stable until the end of treatment. The changes were reversible, as the values returned close to baseline at the safety follow-up visit.

A dose-dependent increase in mean and median plasma antithrombin III activity and fibrinogen levels, as well as in the number of participants with high plasma antithrombin III activity and fibrinogen levels, was observed during the study. The clinical relevance of these findings is unclear, as no dose-dependent differences in the frequency of adverse events potentially related to changes in these parameters were observed.

Supplementary Tables and Figures

Supplementary Table S1 MCP-Mod analysis of the primary endpoint: multiplicity-adjusted *p*-values for the four candidate dose–response models using a pre-specified overall type I error rate of α=0.1 (one-sided)

Candidate dose–response model	Multiplicity-adjusted *p*-value
Emax ED_{50}=30	0.035
Emax ED_{50}=50	0.038
Sigmoidal Emax ED_{50}=30; Hill coefficient=3	0.032
Sigmoidal Emax ED_{50}=60; Hill coefficient=5	0.060

Hill coefficient determines the steepness of the model at the ED_{50}

ED_{50} dose giving half of the asymptotic maximum effect, *Emax* asymptotic maximum change from placebo effect

Supplementary Table S2 Prohibited prior and concomitant therapy

Therapy	Time frame
Angiotensin converting enzyme inhibitor	From 12 weeks prior to screening until EoI
Opioids, inducing codeine	From 2 weeks prior to screening until EoI
Digoxin	From 2 weeks prior to screening until 2 weeks after EoI
Dabigatran	From 2 weeks prior to screening until 2 weeks after EoI
Apixaban	From 2 weeks prior to screening until 2 weeks after EoI
Edoxaban	From 2 weeks prior to screening until 2 weeks after EoI
Gabapentin/pregabalin (for RCC)	From 2 weeks prior to screening until EoI
Tricyclic antidepressants (i.e., amitriptyline, nortriptyline) (indication RCC)	From 4 weeks prior to screening until EoI
Interferon alpha-2b and alpha-2a	From 2 weeks prior to screening until EoI
Mycophenolate mofetil	From 1 week prior to screening until EoI
Methotrexate	From 4 weeks prior to screening until EoI
Ribavirin	From 2 weeks prior to screening until EoI
Non-narcotic cough medicine (including over-the-counter and herbal)	From 1 week prior to screening until EoI
Strong CYP3A4 inhibitors including: • Antivirals (e.g., Viekira Pak, telaprevir, boceprevir) • Protease inhibitors (e.g., ritonavir, lopinavir, indinavir, nelfinavir, saquinavir) • Antifungals (e.g., itraconazole, voriconazole, posaconazole)	From 2 weeks prior to screening until EoI

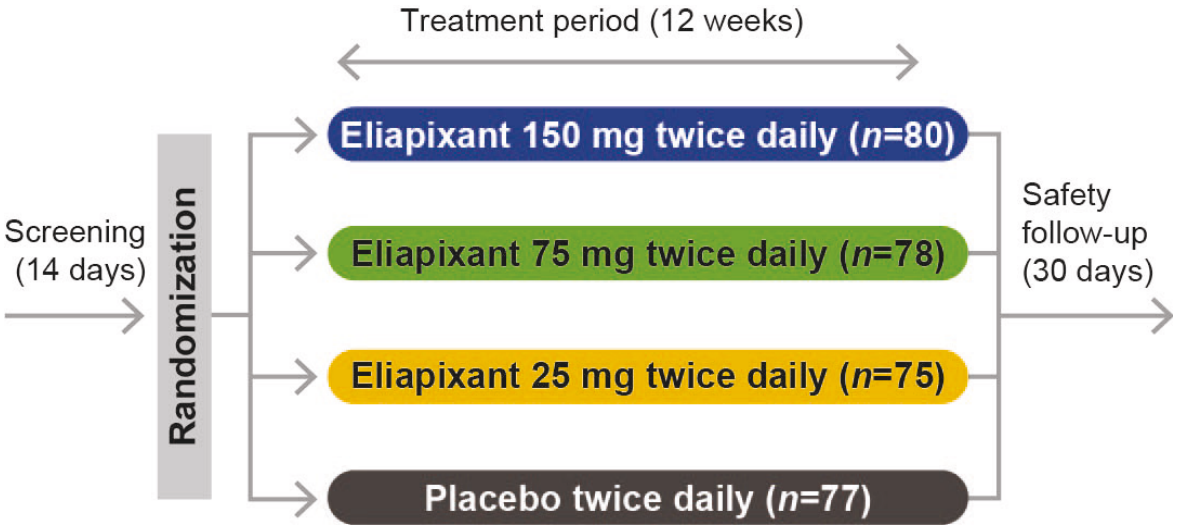
• Antibiotics (e.g., clarithromycin, telithromycin)	
Grapefruit and any grapefruit-containing food products (e.g., grapefruit juice)	
Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's Wort)	From 2 weeks prior to screening until EoI
Non-drug treatment for RCC	
Speech therapy	From 4 weeks prior to screening until EoI
Chinese medicine	From 4 weeks prior to screening until EoI

CYP3A4 cytochrome P450 isoenzyme 3A4, *EoI* end of intervention, *RCC* refractory chronic cough

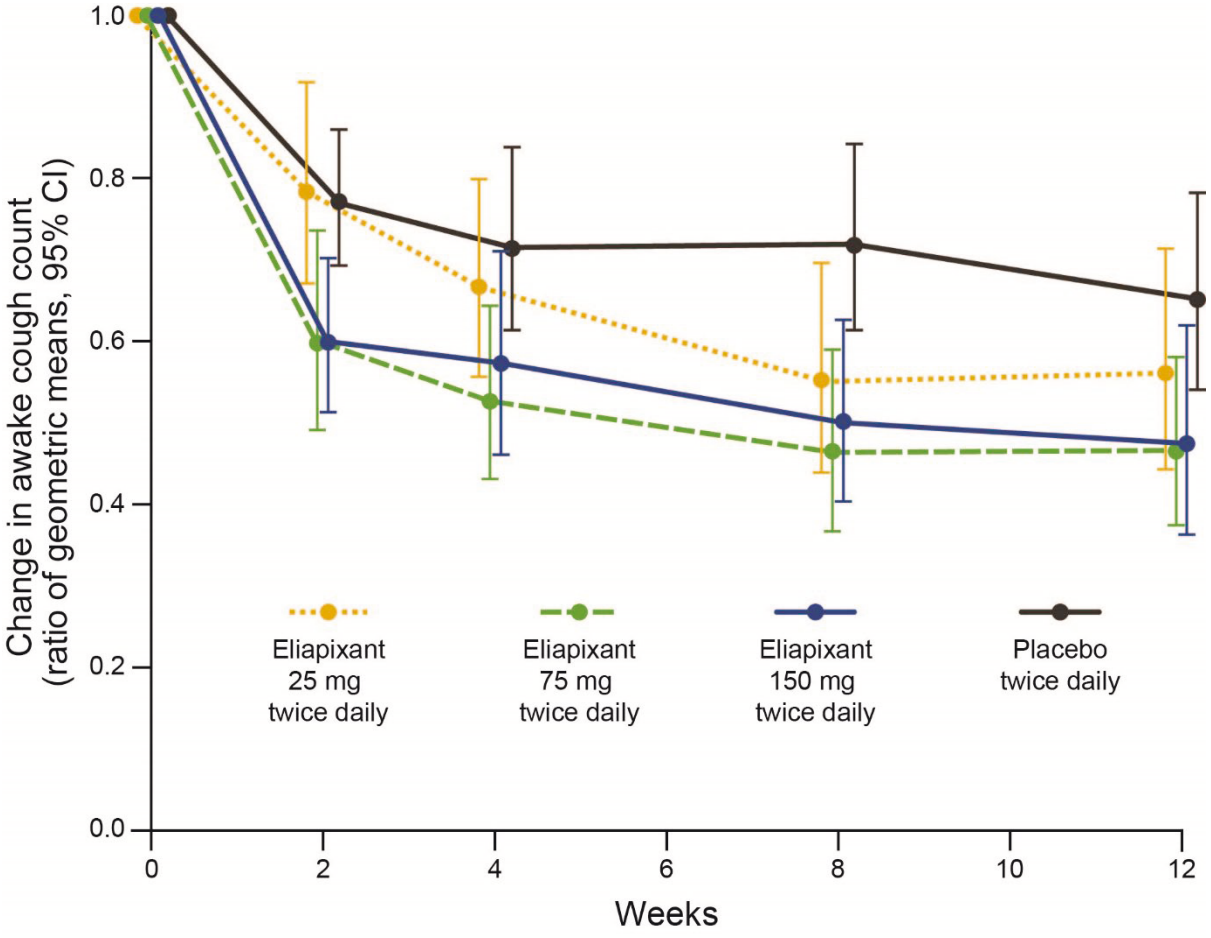
Supplementary Table S3 Medication permitted on stable dose

Therapy	Time frame
Benzodiazepines	From 4 weeks prior to screening until EoI
Paroxetine	From 4 weeks prior to screening until EoI
Baclofen	From 4 weeks prior to screening until EoI
Memantine	From 4 weeks prior to screening until EoI
Azithromycin and erythromycin	From 4 weeks prior to screening until EoI
Antihistamines (chlorphenamine) for RCC	From 4 weeks prior to screening until EoI
Gabapentin/pregabalin (other indications, e.g., diabetic neuropathy, neuropathic pain)	From 4 weeks prior to screening until EoI
Tricyclic antidepressants (i.e., amitriptyline, nortriptyline) (other indications)	From 4 weeks prior to screening until EoI
Asthma medications (e.g., inhaled corticosteroids, leukotriene modifiers, long-acting beta agonists, theophylline)	From 4 weeks prior to screening until EoI
Proton-pump inhibitors	From 8 weeks prior to screening until EoI

EoI end of intervention, *RCC* refractory chronic cough

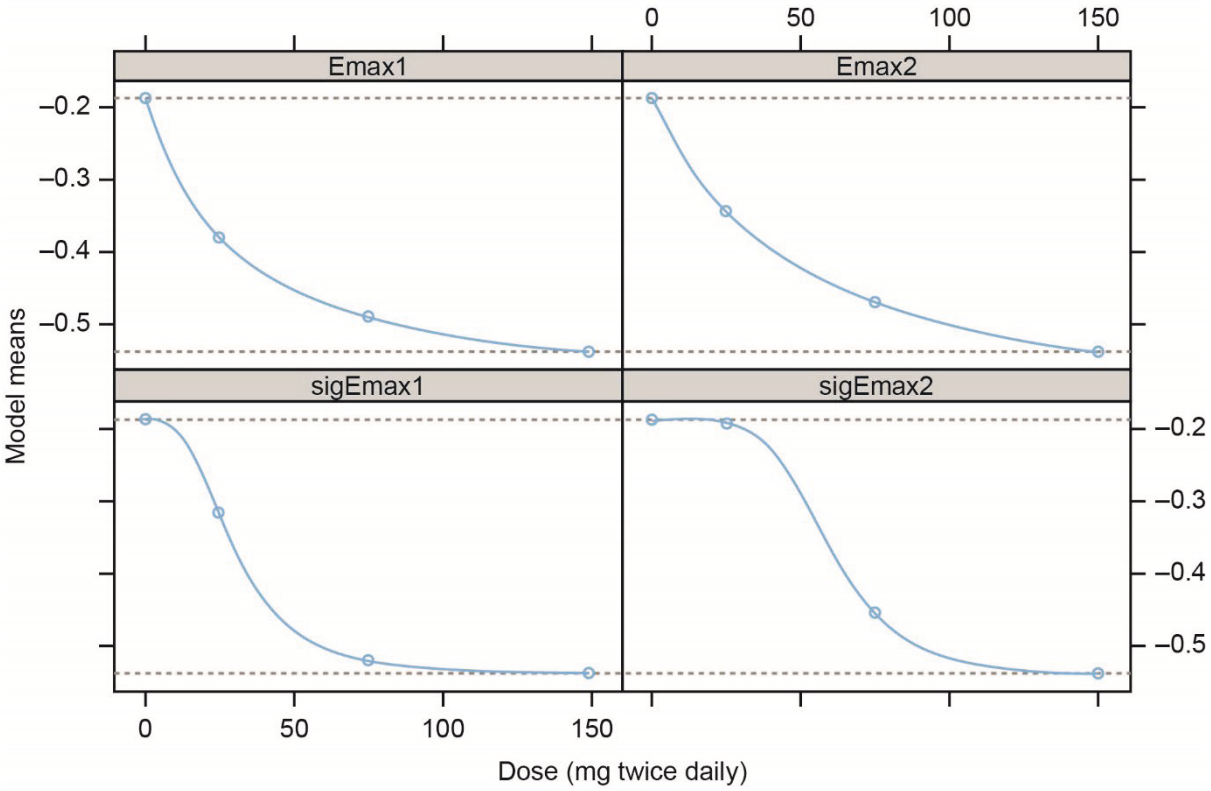


Supplementary Fig. S1 PAGANINI study design. *N* numbers show the treatment allocation for the full and safety analysis set



Supplementary Fig. S2 Change from baseline of awake cough count by visit (per protocol set). *CI* confidence interval

Model	Parameters			
	E_0	ED_{50}	Emax	Hill coefficient
Emax1	–0.19	30	–0.42	N/A
Emax2	–0.19	50	–0.47	N/A
Sigmoidal Emax1	–0.19	30	–0.35	3
Sigmoidal Emax2	–0.19	60	–0.35	5



Supplementary Fig. S3 Parameters of the dose–response candidate models and the candidate set of dose–response curves. The Hill coefficient determines the steepness of the model at the ED_{50}, For the parameters: E_0 placebo effect, ED_{50} dose giving half of the asymptotic maximum effect, *Emax* asymptotic maximum change from placebo effect, *N/A* not applicable.

Supplementary References

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