Early View

Original research article

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Akio Niimi[1], Junpei Saito[2], Tadashi Kamei[3], Masaharu Shinkai[4], Hiroyuki Ishihara[5], Mitsuaki Machida[5] and Sayaka Miyazaki[5]

Affiliations:

[1]Department of Respiratory Medicine, Allergy and Clinical Immunology, Nagoya City University, Aichi, Japan

[2]Department of Pulmonary Medicine, Fukushima Medical University, Fukushima, Japan

[3]Department of Respiratory Medicine, Kamei Internal Medicine and Respiratory Clinic, Kagawa, Japan

[4]Respiratory Medicine, Tokyo Shinagawa Hospital, Tokyo, Japan

[5]Shionogi & Co., Ltd., Osaka, Japan

Correspondence:

Sayaka Miyazaki, MS

9F Nissay Yodoyabashi East, 3-13, Imabashi 3-chome, Chuo-ku, 541-0042 Osaka, Japan

Tel: +81-6-6202-2161

Fax: +81-6-6202-2239

E-mail: sayaka.miyazaki@shionogi.co.jp

Summary

This study shows the efficacy of a highly selective P2X$_3$ receptor antagonist to reduce cough frequency, with low incidence of taste disturbance. Sivopixant may be a promising therapeutic option for refractory or unexplained chronic cough.

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STATISTICAL SUMMARY

Abstract Text	Manuscript Text (Intro - Disc)	References	Figures/Tables
N = 226 (Limit = 250)	N = 3352 (Limit = 3000)	N = 30 (Limit = 40)	N = 8 (Limit = 8)

ABSTRACT

Background: The purinoceptor subtype $P2X_3$ has been shown to have significant involvement in the cough reflex; the heterotrimer version of the purinoceptor ($P2X_{2/3}$) has been implicated in taste disturbance. The most advanced clinical candidate antagonist gefapixant has low selectivity among $P2X_3$ receptors and induced taste disturbance, whereas newly developed sivopixant has high selectivity towards $P2X_3$ *versus* $P2X_{2/3}$.

Methods: In a phase 2a, randomised, double-blind, placebo-controlled, crossover, multicentre study, adult patients with refractory or unexplained chronic cough received oral sivopixant 150 mg or placebo once daily for 2 weeks, followed by a 2–3-week washout period, and then crossed over to placebo or sivopixant for 2 weeks. Efficacy and safety of sivopixant were evaluated.

Results: Of 31 randomised patients, 15 in the sivopixant-first group and 15 in the placebo-first group completed the study. After 2 weeks' treatment, the placebo-adjusted ratios of the average hourly number of coughs to baseline during daytime (primary endpoint) and over 24 hours (secondary endpoint) were −31.6% (p=0.0546) and −30.9% (p=0.0386), respectively. Sivopixant also improved health-related quality of life. Treatment-related adverse events occurred in 12.9% and 3.2% of patients during sivopixant and placebo administration, respectively. Mild taste disturbance occurred in two patients (6.5%) during sivopixant administration.

Conclusions: Sivopixant reduced objective cough frequency and improved health-related quality of life, with a low incidence of taste disturbance, among patients with refractory or unexplained chronic cough.

Introduction

Chronic cough, defined as cough lasting for more than 8 weeks, affects approximately 10% of the general population in the world, although there is considerable variability (2–18%) [1, 2]. This persistent and irritating condition may cause impaired quality of life and various comorbidities, including incontinence, cough syncope and rib fractures [3]. Chronic cough may be due to a wide variety of conditions, with a small subset of patients not having an identifiable cause designated as unexplained chronic cough [4, 5]. Most cases of refractory or unexplained chronic cough (R/UCC) are considered to have a common pathophysiology of cough refractoriness, also known as cough hypersensitivity syndrome, due to either peripheral and/or central sensitivity [6]. At present, there is a scarcity of highly effective and tolerable antitussives for patients with R/UCC; therefore, there is a need for further research to develop medications for this condition.

The purinoceptor subtype, $P2X_3$, is an ATP-gated ion channel primarily expressed in small-diameter primary afferent fibres ($A\delta$ and C), which are associated with sensory perception and transmission. This receptor has been shown to have significant involvement in the cough reflex. There are two types of $P2X_3$ receptor: the homotrimer ($P2X_3$) and the heterotrimer ($P2X_{2/3}$). $P2X_{2/3}$ receptors have been implicated in taste disturbance [7]. Gefapixant, the most advanced $P2X_3$ receptor antagonist in the clinical development pipeline, has three- to eight-fold selectivity for the $P2X_3$ receptor compared with the $P2X_{2/3}$ receptor (50% inhibitory concentrations of 30 nM for $P2X_3$ and 100–250 nM for $P2X_{2/3}$) [8]. In a clinical trial, gefapixant significantly reduced cough frequency in patients with R/UCC but induced taste disturbance in a dose-dependent manner [9, 10].

Therefore, a compound that is highly selective towards P2X$_3$ receptors with low affinity for P2X$_{2/3}$ receptors might be expected to be effective at inhibiting the cough reflex, with a low incidence of taste disturbance.

Sivopixant (S-600918) is a newly developed compound that has high selectivity towards P2X$_3$ receptors (*versus* P2X$_{2/3}$ receptors) in the peripheral nervous system. Through structure-activity relationship studies, sivopixant has been identified as having highly selective antagonistic activity (50% inhibitory concentrations of 4.2 nM for P2X$_3$ receptors and 1100 nM for P2X$_{2/3}$ receptors) and favourable pharmacokinetic profiles [11].

Therefore, we conducted a sivopixant proof-of-concept study for R/UCC to evaluate the efficacy and safety of sivopixant administration for 2 weeks in patients with R/UCC. Some of the results of this study have been previously reported in the form of abstracts [12-15].

Methods

Study design and participants

This was a phase 2a, randomised, double-blind, placebo-controlled, crossover study (figure 1) conducted in 18 centres (including 10 specialist clinics) in Japan, and included patients aged 20–75 years with R/UCC lasting for 6 months or more. Patient had a cough severity assessment using a visual analogue scale (VAS) of ≥40 mm and an average subjective cough frequency while awake of ≥10 times per hour during the previous 24 hours for ≥70% of the days during the screening period (1–4 weeks), as recorded in a patient diary. The study was approved by the institutional review board at

each study site and was conducted in accordance with the Declaration of Helsinki. No changes to the protocol were made after trial commencement. All patients gave written informed consent before enrolment. This study is registered with the Japan Pharmaceutical Information Center Clinical Trials Information database (JapicCTI-184027). Patient eligibility criteria, prior drugs, and additional details about study methodology are provided in the supplementary material.

Treatment

Enrolled patients were randomly assigned to either the sivopixant-first group or the placebo-first group using a 1:1 allocation ratio. After randomisation, 150 mg sivopixant (a dose based on phase 1 study results [unpublished data]) or placebo, respectively, was administered orally once daily in the morning for 2 weeks. This was followed by a 2–3-week washout period, and then patients crossed over to placebo or 150 mg sivopixant for 2 weeks. Follow-up observation was performed for 7 days after the last dose of the study drug in the second treatment period.

Outcome measurements

The primary endpoint was the ratio of the average number of coughs per hour in the daytime after 2 weeks' administration of sivopixant to that of baseline. The secondary efficacy endpoints were: the ratio of the average number of coughs per hour in 24 hours, during night-time, while awake and while asleep after 2 weeks' administration of study drug to that of baseline; change in Leicester Cough Questionnaire (LCQ; Japanese version, J-LCQ) [16, 17]; change in mean cough severity as assessed on

VAS; and change in EuroQol Questionnaire-5 Dimensions-5 Levels (EQ-5D-5L™) (Japanese version) [18] and EuroQol VAS (EQ-VAS).

The objective frequency of cough was measured using data collected from a VitaloJAK™ (Vitalograph, Buckingham, UK) cough monitor device. For J-LCQ, the proportion of patients who achieved the minimum important difference (MID) in total LCQ score (1.3 points) [19] was evaluated.

The safety endpoints were occurrence of adverse events (AEs) and treatment-related AEs and other safety findings, including blood pressure, pulse rate, electrocardiogram and clinical laboratory tests.

Statistical analysis

Continuous data were presented as mean±SD, whereas categorical data were presented as counts and frequencies. The primary outcome, adjusted by placebo, was evaluated by applying a mixed-effect model to the common logarithm of the ratio of the average number of coughs per hour after administration of sivopixant for 2 weeks to that of baseline in each treatment period as a response. The primary efficacy outcome was evaluated in the full analysis set (FAS).

The sample size required to assure 80% power using a two-sided 5% level of significance was calculated to be 26. This was calculated based on the assumptions that the baseline number of coughs was 30, changes from baseline while receiving sivopixant and placebo were −18 and −3, respectively, and an SD of 0.60 on the common logarithmic scale. The final target enrolment was 30. All statistical tests were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

The study was initiated on 20 August 2018 and ended on 20 February 2019. A total of 31 patients were enrolled in the study and randomly assigned to the sivopixant-first group (n=16) and the placebo-first group (n=15) (figure 2). Of these, 15 in the sivopixant-first group and 15 in the placebo-first group completed the study. The FAS included all 31 randomised patients. One patient in the sivopixant-first group was withdrawn from the study because of tension headache and positional vertigo during placebo administration.

Women accounted for 65% of all included patients (table 1). All patients were Asian. The mean (±SD) age of patients was 50.0±14.6 years, body weight was 62.6±13.9 kg, and body mass index was 24.1±5.0 kg/m^2. The most common underlying disorders in all 31 patients were asthma (45%), cough variant asthma (32%), rhinitis (19%) and gastroesophageal reflux disease (16%) (some patients had two or more underlying disorders). The cough was unexplained in 19% of patients. Twenty-one patients with asthma or cough variant asthma had received prior drug treatments, mainly inhaled corticosteroids/long-acting β-agonists; long-acting muscarinic antagonists or leukotriene receptor antagonists were added, as appropriate (supplemental table S1). The mean duration of cough was 97.6±102.3 months. The mean forced expiratory volume in 1 second/forced expiratory vital capacity was 82.1±7.5%. The difference in baseline characteristics between the sivopixant-first and placebo-first groups was not statistically significant. The baseline cough frequencies according to the treatment received are reported in table 2.

Efficacy

For the primary efficacy outcome, the ratio of the average number of coughs per hour during daytime after 2 weeks' administration of the study drug to that of baseline (primary endpoint) was −54.1% for sivopixant administration and −33.0% for placebo. When adjusted by placebo, the ratio of the average hourly cough frequency during daytime after 2 weeks' sivopixant administration to that of baseline was −31.6% (95% CI −53.6 to 0.8; p=0.0546; table 2). The individual patient data are shown in figure 3. Statistical analysis showed that order effect (p=0.8863) and period effect (p=0.7238) were not observed, and the number of coughs decreased in the sivopixant group during the second treatment period. However, the number of coughs per hour in the daytime at baseline in the second treatment period (mean of 30.4 in the sivopixant-first group, 36.6 in the placebo-first group) was lower than the number at baseline in the first treatment period (mean of 53.4 in the sivopixant-first group, 59.1 in the placebo-first group) and did not return to the baseline levels of the first treatment period (supplemental table S2). The ratio of the average number of coughs per hour in the 24 hours after 2 weeks' administration to that of baseline was −52.6% for sivopixant and −31.4% for placebo (table 2). Adjusted by placebo, the ratio of the average hourly cough frequency in 24 hours after 2 weeks' sivopixant administration to that of baseline was −30.9% (95% CI −51.3 to −2.1; p=0.0386, figure 3). As for cough during night-time, while awake and while asleep, the placebo-adjusted ratios of the average number of coughs per hour after 2 weeks' sivopixant administration to that of baseline were lower than those after placebo administration, but the differences were not statistically significant (table 2).

The change in J-LCQ total score from baseline after 2 weeks was 2.46 and 1.06 after sivopixant and placebo administration, respectively, and the difference (sivopixant minus placebo) was 1.40 (95% CI 0.06–2.75; p=0.0415) (table 3, figure 3). The proportion of patients who had an increase in the total J-LCQ scores by at least the MID was 58.1% (95% CI 39.1–75.5) for sivopixant compared with 35.5% (95% CI 19.2–54.6) for placebo. The change in cough severity by VAS after 2 weeks was −18.8 mm after sivopixant administration and −12.4 mm after placebo (difference of −6.4 mm; 95% CI −14.8 to 2.0; p=0.1334).

For EQ-5D-5L score, the change from baseline after 2 weeks' administration was 0.10 and 0.01 after sivopixant and placebo, respectively, and the difference (sivopixant minus placebo) was 0.09 (95% CI 0.03–0.16; p=0.0082). For EQ-VAS, the change from baseline after 2 weeks' administration was 11.4 and 2.8 after sivopixant and placebo, respectively, and the difference (sivopixant minus placebo) was 8.6 (95% CI 1.0–16.2; p=0.0274).

The per protocol set (PPS) analysis consisted of 24 patients: 13 in the sivopixant-first group and 11 in the placebo-first group. The most common reason for exclusion from the PPS was administration of prohibited concomitant therapy (n=4). In addition, in one patient, the cough monitor recording stopped during measurement, and another patient had no cough monitor data in the second period owing to discontinuation from the study.

For the PPS, the ratio of the average number of coughs per hour during daytime after 2 weeks' administration of the study drug to that of baseline was −54.8% and −37.5% for sivopixant and placebo, respectively. When adjusted by placebo, the ratio of the

average hourly cough frequency during daytime after 2 weeks' sivopixant administration to that of baseline was −27.7% (95% CI −52.6 to 10.4; p=0.1263).

Safety

The safety analysis population included all 31 randomised patients. Treatment-emergent AEs (TEAEs) occurred in 35.5% (11/31) of patients during sivopixant administration and in 29.0% (9/31) during placebo administration (table 4). One patient had two TEAEs (tension headache and positional vertigo) leading to discontinuation of the study drug during placebo administration. All TEAEs occurred in one or two patients, except for contact dermatitis related to the cough monitor device adhesive tape application (three patients during sivopixant administration and one during placebo administration; two of these patients were treated with topical corticosteroids, and the others recovered spontaneously without any treatment).

Treatment-related AEs occurred in 12.9% (4/31) of patients during sivopixant administration and 3.2% (1/31) of patients during placebo administration (table 5). Treatment-related AEs of dysgeusia, hypogeusia, oral hypoesthesia and drug-induced liver injury occurred in one patient each during sivopixant administration. Oral hypoesthesia occurred in one patient during placebo administration. No deaths were reported. However, one serious AE of bursitis occurred in one patient during placebo administration (table 4).

Changes in mean laboratory values, blood pressure and pulse rate were generally modest, and there were no clinically notable trends over time during either sivopixant or placebo administration (data not shown). No clinically significant electrocardiogram findings were reported.

One patient (3.2%) experienced liver injury during sivopixant administration. This patient had a history of cholelithiasis and hepatic steatosis and was receiving ursodeoxycholic acid treatment for cholelithiasis during the study. Alanine aminotransferase and aspartate aminotransferase levels increased in this patient (although to <1.8 times the upper limit of normal) during the first week of sivopixant administration but decreased to normal levels by the second week of drug administration. Treatment was continued and the patient recovered without specific treatment.

Discussion

This crossover study is the first clinical study to evaluate the efficacy and safety of sivopixant, a highly selective $P2X_3$ receptor antagonist, in patients with R/UCC. The study showed that the change from baseline in the number of coughs per hour during daytime after 2 weeks' sivopixant administration (primary endpoint) was greater than after placebo. However, the placebo-adjusted difference was not statistically significant and the primary endpoint was not met. In contrast, statistical significance between sivopixant and placebo was observed in the number of coughs per hour over 24 hours, and sivopixant improved subjective J-LCQ. Very few mild taste disturbance TEAEs were observed, and no patient discontinued because of taste disturbance.

The placebo-adjusted cough frequency ratios reported with sivopixant translated to values similar to those reported in other $P2X_3$ receptor antagonist trials. A randomised, double-blind, controlled, parallel-group, phase 2b trial found that twice-daily gefapixant 7.5 mg, 20 mg and 50 mg resulted in changes in the frequency of awake cough of between −22.0% (95% CI −41.8 to 4.6; p=0.097) with 7.5 mg and −37.0% (95% CI

−53.3 to −14.9; p=0.0027) with 50 mg compared with placebo [9]. However, because of the role of the P2X$_3$ receptor in taste perception, taste disturbance is one of the most commonly reported AEs associated with P2X$_3$ receptor antagonists. SMITH *et al.* showed that, depending on the dose, 10–81% of gefapixant-treated patients reported taste-related AEs (dysgeusia, hypogeusia or ageusia) [9]. With a 50-mg dose – the minimum dose that reported significant improvement in the primary efficacy outcome – 48% of patients reported dysgeusia, 24% hypogeusia and 21% ageusia during gefapixant treatment [9]. In the study, taste-related TEAEs led to treatment discontinuation in 16% of those receiving the highest dose administered [20]. Another randomised, double-blind, placebo-controlled, crossover, dose-escalation study, which reported that gefapixant doses ≥30 mg produced maximal improvements in cough frequency compared with placebo (p<0.05), also confirmed that taste disturbance occurred in a dose-dependent manner [10]. For sivopixant, the proportion of patients who reported taste disturbance in the present study was low (2/31; 6.5%). Furthermore, no patient discontinued treatment due to taste-related TEAEs.

Low rates of taste-related TEAEs are advantageous as drug-induced taste disturbance has been known to impair food intake and reduce quality of life and treatment adherence [21, 22]. The low rate of taste disturbance could be attributed to the specificity of the drug to P2X$_3$ with low affinity for P2X$_{2/3}$. Specific blockade of P2X$_3$ receptors is not expected to result in marked impairment in taste perception owing to the more prominent role of P2X$_{2/3}$ in taste perception and transmission, the lower proportion of P2X$_3$ receptors compared with P2X$_2$ receptors in taste buds, and possible

channel redundancies involved in the transduction of taste bud responses [7, 23]. This was also suggested by a recent manuscript of the other $P2X_3$ selective antagonist [24]. In this study, the ratio of the number of coughs per hour in 24 hours after sivopixant administration to that of baseline was significantly lower than that after placebo (p=0.0386). However, the ratios from baseline in the number of coughs per hour during daytime, night-time, while awake and while asleep after 2 weeks' sivopixant administration were lower than those after placebo, although the differences *versus* those with placebo were not statistically significant. One reason for the lack of statistically significant differences with these outcomes could be insufficient sample size. In general, chronic cough is more prominent during the day; hence, treatment-related improvements in cough are expected to be more prominent during the day, making it the rational basis for sample size computation. As expected, the placebo-adjusted reduction in the average hourly cough frequency was higher for daytime cough than for a 24-hour period in this study (table 2). However, variability was higher for daytime cough than a 24-hour period cough, which might have affected the result. Our results (figure 3) showed that 24-hour cough frequency might be the optimum endpoint for drug efficacy studies, and that the use of daytime/awake cough frequency might miss the clinical efficacy of the treatment.

The improvements in cough frequency translated to improvements in subjective measures. The placebo-adjusted changes associated with 2-week administration of sivopixant were statistically significant in terms of J-LCQ score (p=0.0415), EQ-5D-5L score (p=0.0082) and EQ-VAS (p=0.0274). Furthermore, 58.1% of patients achieved the MID in LCQ score with sivopixant compared with 35.5% for placebo. In general,

significant improvements in quality-of-life measurements could be attributed to not only improvements in cough frequency but also cough intensity. Although not objectively assessed, an improvement in cough intensity may be hypothesised for this study.

In this study, we observed that the number of coughs was reduced by approximately 30% when patients received placebo in the daytime, over 24 hours, or while awake. A similar placebo effect was observed in previous studies, including a phase 2b study of gefapixant [9], and the placebo effect in the phase 3 study of gefapixant was even greater [25]. It may not be appropriate to compare the current results with those from previous studies, but it would be impossible to avoid the placebo effect as this is a characteristic of these kinds of studies. The cause of the placebo effect in this study has not been identified; however, the previously disclosed positive results from clinical studies of gefapixant might have led patients to have high expectations for a new treatment for chronic cough, thereby contributing to the placebo effect observed in this study. In fact, a similar suggestion was made in the report of a phase 2b study of gefapixant [9].

One of the limitations of this study is its crossover design, the disadvantages of which include some potential for carryover effect. The duration of the washout period was decided based on the antitussive effect of sivopixant, which was not considered to be attributable to any organic changes, and the half-life of a single 150-mg dose of sivopixant, with the assumption that the plasma sivopixant concentration would be sufficiently low after 1 week. Therefore, we believe the washout period was sufficient to minimise any carryover effects. In fact, statistical analysis showed that order effect and period effect were not observed, which suggests a low probability for carryover effect.

Other limitations include the small number of enrolled patients and the inclusion of only Asian patients and only one country (Japan). In addition, the causes and mechanisms of cough differ from patient to patient; hence, it may be expected that different cough aetiologies would have varying responses to $P2X_3$ antagonism in the present cohort. In this study, 45% of patients had asthma and 32% had cough variant asthma (77% in total). These rates for asthma-related cough are higher than those reported in other studies [26]. Asthma-related cough, compared with non-asthmatic chronic cough, is characterised by relative predominance of cough during night-time [27-29]. This might lower the relative event rate of daytime cough compared with other studies. In addition, the dose used in this trial was not selected based on data from a clinical efficacy dose ranging study. To determine the optimal clinical dose, a dose ranging study has been conducted in patients with R/UCC (NCT04110054).

In conclusion, although the results of this phase 2 study should be viewed with caution as the primary endpoint was not achieved, sivopixant can be effective in R/UCC for reducing cough frequency as well as improving health-related quality of life, with very few taste disturbance AEs. We recommend further studies, such as dose-finding studies and parallel-group phase 3 trials, which include a larger number of patients from various races and countries.

Author contributions: A. Niimi, H. Ishihara, M. Machida and S. Miyazaki made a contribution to the concept or design of the study. J. Saito, T. Kamei and M. Shinkai participated in data collection. A. Niimi, J. Saito, T. Kamei, M. Shinkai, H. Ishihara, M. Machida and S. Miyazaki were responsible for producing the initial draft of the paper. M. Machida carried out the primary statistical analysis. A. Niimi, J. Saito, T. Kamei, M. Shinkai, H. Ishihara, M. Machida and S. Miyazaki provided written comments and feedback during manuscript development and were directly involved in the execution of the study. All authors approved the final draft of the manuscript.

Conflict of interest: H. Ishihara, M. Machida and S. Miyazaki are employed by Shionogi & Co., Ltd. and are minor stock holders of Shionogi & Co., Ltd. A. Niimi, J. Saito, T. Kamei and M. Shinkai have nothing to disclose.

References

1.   Song WJ, Chang YS, Faruqi S*, et al.* The global epidemiology of chronic cough in adults: a systematic review and meta-analysis. *Eur Respir J* 2015; 45(5): 1479–1481.

2.   Alhajjaj MS, Bajaj P. Chronic Cough. In: StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK430791/. Date last updated: July 17, 2020. Date last accessed: February 22, 2021.

3.   Chamberlain SA, Garrod R, Douiri A*, et al.* The impact of chronic cough: a cross-sectional European survey. *Lung* 2015; 193(3): 401–408.

4.   Morice AH, Millqvist E, Bieksiene K*, et al.* ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J* 2020; 55(1): 1901136.

5.   Spanevello A, Beghe B, Visca D*, et al.* Chronic cough in adults. *Eur J Intern Med* 2020; 78: 8–16.

6.   Morice AH, Faruqi S, Wright CE*, et al.* Cough hypersensitivity syndrome: a distinct clinical entity. *Lung* 2011; 189(1): 73–79.

7.   Ford AP. In pursuit of P2X3 antagonists: novel therapeutics for chronic pain and afferent sensitization. *Purinergic Signal* 2012; 8(Suppl 1): 3–26.

8.   Ford AP, Undem BJ. The therapeutic promise of ATP antagonism at P2X3 receptors in respiratory and urological disorders. *Front Cell Neurosci* 2013; 7: 267.

9.   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.

10.   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.

11.   Kai H, Horiguchi T, Kameyama T. Dioxotriazine derivatives as a new class of P2X3 receptor antagonists part 2: discovery of clinical candidate S-600918. Abstract presented at: *ACS Fall 2020 Virtual & Meeting Exposition*; August 17-20, 2020; Virtual Meeting. Abstract MEDI 210.

12.   Niimi A, Ishihara H, Hida H*, et al.* Phase 2a randomised, double-blind, placebo-controlled, crossover study of a novel P2X3 receptor antagonist S-600918 in patients with refractory chronic cough. *Eur Respir J* 2019; 54: RCT452.

13.   Niimi A, Ishihara H, Hida H*, et al.* Phase 2a randomized, double-blind, placebo-controlled, crossover study of a P2x3 receptor antagonist S-600918: effects on health-related quality of life in patients with refractory chronic cough. *Am J Respir Crit Care Med* 2020; 201: A7647.

14.   Niimi A, Ishihara H, Hida H. Phase 2a randomized, double-blind, placebo-controlled study of a P2X3 receptor antagonist S-600918 in patients with refractory chronic cough: correlation between changes in cough frequency and Leicester Cough Questionnaire score [Japanese]. Abstract presented at: *Japanese Society of Allergology/World Allergy Organization Joint Congress 2020*; September 17-October 20, 2020; Virtual Meeting.

15.   Niimi A, Ishihara H, Hida H. Phase 2a randomized, double-blind, placebo-controlled, crossover study of a P2X3 antagonist S-600918: effects on health-related quality of life in patients with refractory chronic cough [Japanese]. Encore abstract presented at: *The 22nd Annual Meeting of Japan Cough Society*; September 26-27, 2020; Virtual Meeting.

16.   Birring SS, Prudon B, Carr AJ*, et al.* Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; 58(4): 339–343.

17.   Kanemitsu Y, Niimi A, Matsumoto H*, et al.* Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma. *Allergol Int* 2016; 65(3): 320–326.

18.   Shiroiwa T, Ikeda S, Noto S*, et al.* Comparison of value set based on DCE and/or TTO data: scoring for EQ-5D-5L health states in Japan. *Value Health* 2016; 19(5): 648–654.

19.   Raj AA, Pavord DI, Birring SS. Clinical cough IV:what is the minimal important difference for the Leicester Cough Questionnaire? *Handb Exp Pharmacol* 2009; 187: 311–320.

20.   Irwin RS, French CL, Madison JM. Managing unexplained chronic cough in adults: what are the unmet needs? *Lancet Respir Med* 2020; 8(8): 745–747.

21.   Wang T, Glendinning J, Grushka M*, et al.* From the Cover: Drug-Induced Taste Disorders in Clinical Practice and Preclinical Safety Evaluation. *Toxicol Sci* 2017; 156(2): 315–324.

22.   Schiffman SS. Influence of medications on taste and smell. *World J Otorhinolaryngol Head Neck Surg* 2018; 4(1): 84–91.

23.   Vandenbeuch A, Larson ED, Anderson CB*, et al.* Postsynaptic P2X3-containing receptors in gustatory nerve fibres mediate responses to all taste qualities in mice. *J Physiol* 2015; 593(5): 1113–1125.

24.   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; 2004240.

25.   Merck & Co., Inc. News release: Merck's gefapixant (45 mg twice daily) signicantly decreased cough frequency compared to placebo at week 12 and 24 in patients with refractory or unexplained chronic cough. Data from phase 3 COUGH-1 AND COUGH-2 trials presented at the virtual European Respiratory Society (ERS) International Congress 2020. https://www.merck.com/news/mercks-gefapixant-45-mg-twice-daily-significantly-decreased-cough-frequency-compared-to-placebo-at-week-12-and-24-in-patients-with-refractory-or-unexplained-chronic-cough/. Date last updated: September 8, 2020. Date last accessed: May 28, 2021.

26.   Morice AH, Kastelik JA. Cough. 1: Chronic cough in adults. *Thorax* 2003; 58(10): 901–907.

27.   Niimi A, Fukumitsu K, Takeda N*, et al.* Interfering with airway nerves in cough associated with asthma. *Pulm Pharmacol Ther* 2019; 59: 101854.

28.   Braghiroli A, Braido F, Piraino A*, et al.* Day and night control of COPD and role of pharmacotherapy: a review. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 1269–1285.

29.   Fukuhara A, Saito J, Birring SS*, et al.* Clinical characteristics of cough frequency patterns in patients with and without asthma. *J Allergy Clin Immunol Pract* 2020; 8(2): 654–661.

30.   Mukae H, Kaneko T, Obase Y*, et al.* The Japanese respiratory society guidelines for the management of cough and sputum (digest edition). *Respiratory Investigation* 2021; 59(3): 270–290.
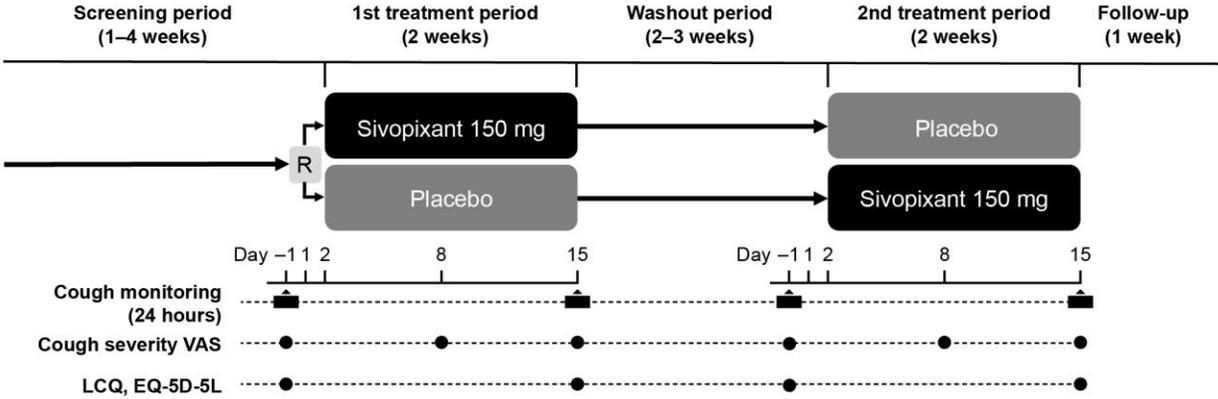
Figure legends

FIGURE 1 Study design.

Day 1 is the day immediately after day –1.

EQ-5D-5L: EuroQol Questionnaire-5 Dimensions-5 Levels; LCQ: Leicester Cough

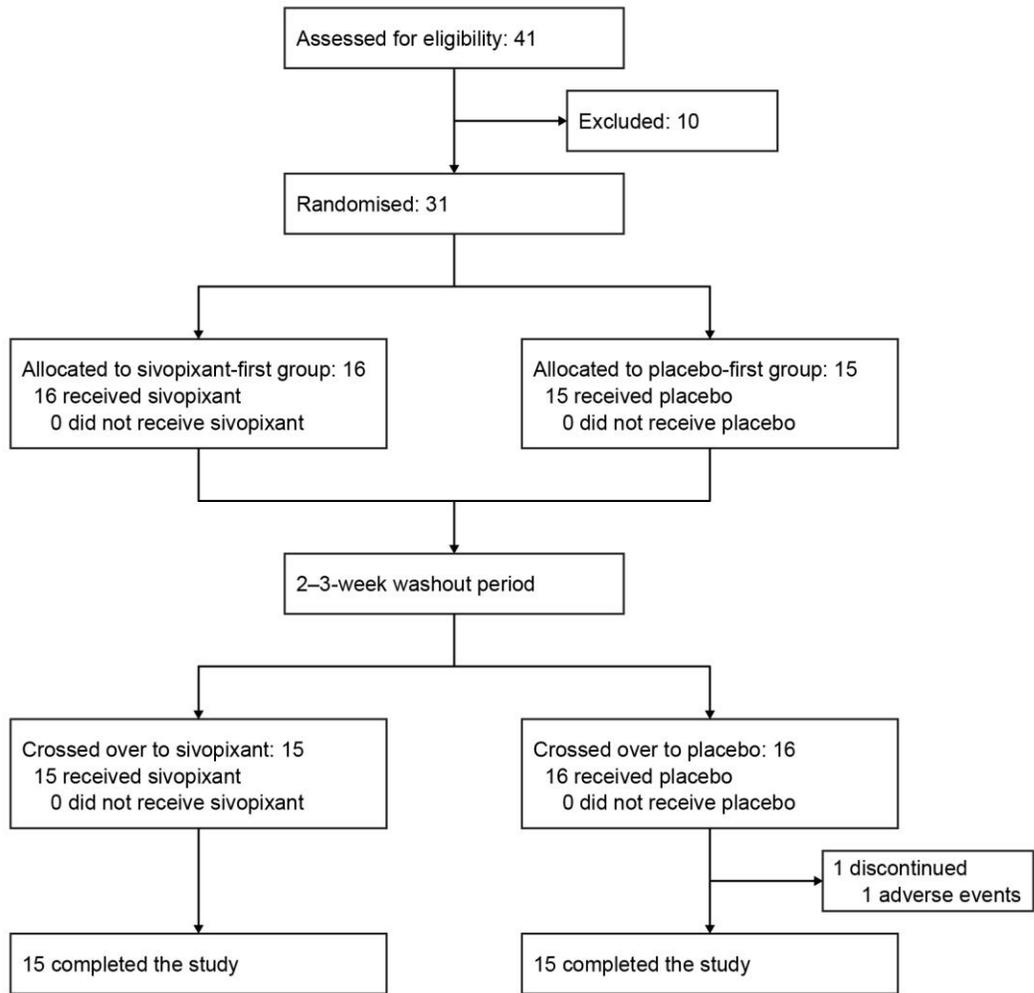Questionnaire; R: randomised on day 1; VAS: visual analogue scale.

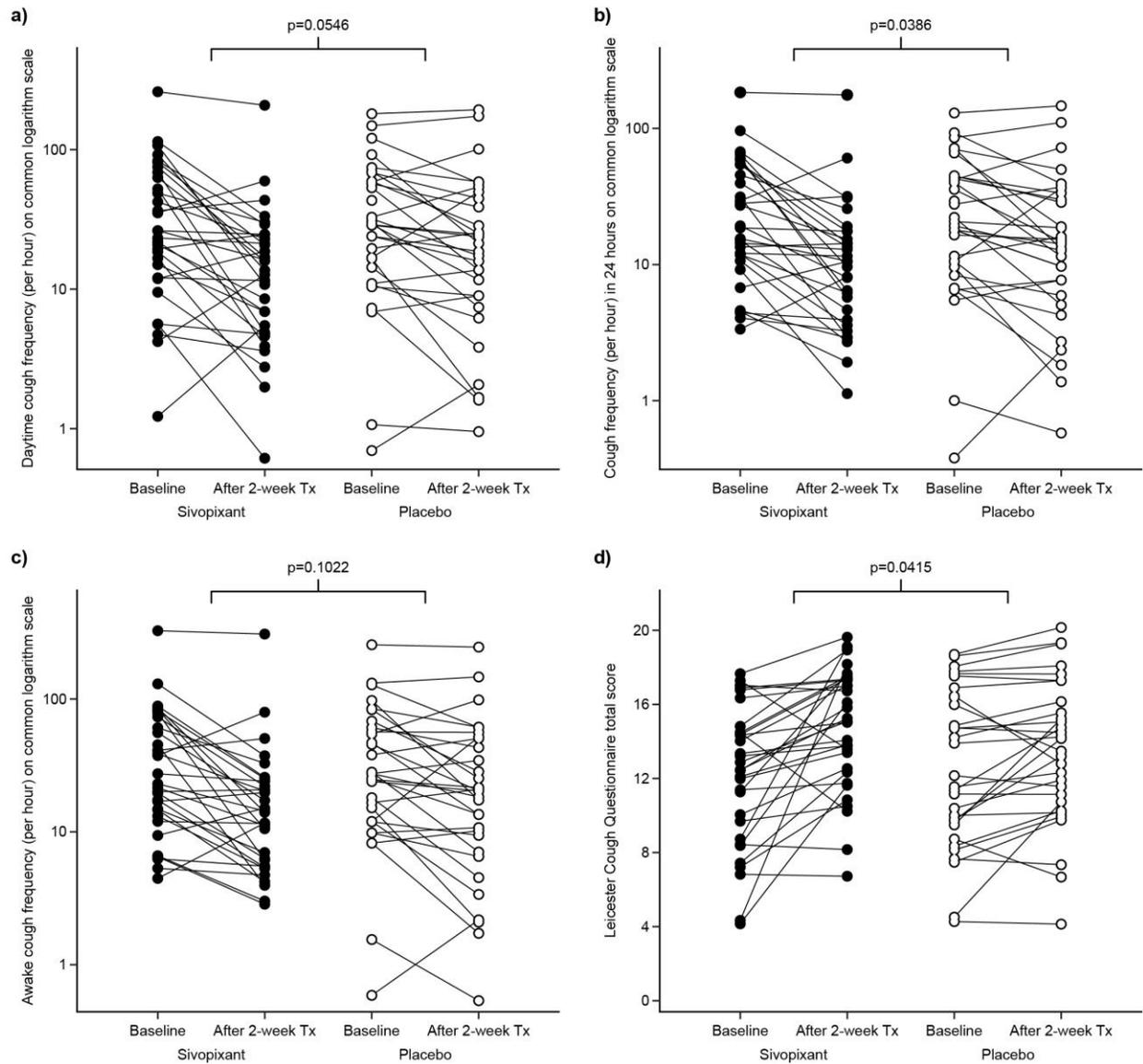**FIGURE 2** Patient flow.

FIGURE 3 Individual plots of cough frequency in the daytime (a), over 24 hours (b), and while awake (c), and LCQ total score (d).

p-values are for the group-level placebo-adjusted differences between sivopixant and placebo in the change from baseline at 2 weeks (see tables 2 and 3).

LCQ: Leicester Cough Questionnaire; Tx: treatment.

TABLE 1 Baseline characteristics of included patients

	Sivopixant-first (n=16)	Placebo-first (n=15)	Total (N=31)
Sex, female	13 (81)	7 (47)	20 (65)
Age, years	53.3±14.0	46.6±15.0	50.0±14.6
20–<65	12 (75)	13 (87)	25 (81)
65–≤75	4 (25)	2 (13)	6 (19)
Weight, kg	62.3±12.6	62.9±15.5	62.6±13.9
Body mass index, kg/m^2	24.6±4.9	23.4±5.2	24.1±5.0
Underlying disorders[#]			
Asthma	10 (63)	4 (27)	14 (45)
Cough variant asthma	4 (25)	6 (40)	10 (32)
Atopic cough[¶]	1 (6)	0	1 (3)
Gastroesophageal reflux disease	3 (19)	2 (13)	5 (16)
Laryngeal allergy[¶]	1 (6)	0	1 (3)
Post-nasal drip	2 (13)	1 (7)	3 (10)
Rhinitis	3 (19)	3 (20)	6 (19)
Sinobronchial syndrome	0	1 (7)	1 (3)
Unexplained cough	2 (13)	4 (27)	6 (19)
Duration of chronic cough, months	102.5±100.1	92.4±107.7	97.6±102.3
FEV$_1$/FVC, %	81.2±8.7	83.0±6.2	82.1±7.5

Data are presented as mean±SD or n (%) unless otherwise stated.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

#Some patients may have more than one underlying disorder.

¶According to the Japanese Respiratory Society guidelines [30], a chronic laryngeal allergy and atopic cough are defined as "Type I chronic allergic diseases that are localized in the center of the larynx and the trachea to the main bronchus, respectively. Chronic laryngeal allergies can be classified into a seasonal laryngeal allergy or perennial laryngeal allergy according to the causative antigens".

TABLE 2 Changes in cough frequency (full analysis set)

	Baseline number of coughs per hour, geometric mean (95% CI)		Ratio (%) at 2 weeks *versus* baseline, mean (95% CI)		Placebo-adjusted difference at 2 weeks	
	Sivopixant	Placebo	Sivopixant	Placebo	Difference, % (95% CI)	p-value
Daytime	25.9 (16.9–39.8)	26.1 (16.6–41.2)	−54.1 (−66.7 to −36.8)	−33.0 (−51.6 to −7.2)	−31.6 (−53.6 to 0.8)	0.0546
24 hours	20.0 (13.7–29.3)	18.9 (11.9–30.2)	−52.6 (−64.7 to −36.3)	−31.4 (−49.1 to −7.4)	−30.9 (−51.3 to −2.1)	0.0386
Night-time	8.8 (5.3–14.7)	9.5 (5.7–15.8)	−45.2 (−60.7 to −23.5)	−22.7 (−44.8 to 8.4)	−29.1 (−53.6 to 8.3)	0.1074
Awake	27.3 (18.5–40.3)	26.2 (16.5–41.5)	−50.5 (−63.1 to −33.5)	−33.3 (−50.5 to −10.0)	−25.8 (−48.3 to 6.5)	0.1022
Asleep	2.5 (1.4–4.7)	1.6 (0.8–3.3)	−14.8 (−48.3 to 40.6)	7.9 (−35.1 to 79.6)	−21.0 (−57.1 to 45.2)	0.4346

TABLE 3 Changes in subjective measures after 2 weeks from baseline

	Baseline (mean±SD)		Change from baseline, mean (95% CI)		Placebo-adjusted difference at 2 weeks	
	Sivopixant	Placebo	Sivopixant	Placebo	Difference (95% CI)	p-value
LCQ[#] total score	12.1±3.8	12.6± 4.2	2.46 (1.51–3.41)	1.06 (0.11– 2.01)	1.40 (0.06–2.75)	0.0415
EQ-5D-5L[#] score	0.7830±0.1 956	0.8166±0 .2285	0.10 (0.06–0.15)	0.01 (−0.04 to 0.06)	0.09 (0.03–0.16)	0.0082
EQ-VAS	58.6±24.7	64.5±24. 0	11.4 (5.5–17.4)	2.8 (−3.1 to 8.7)	8.6 (1.0–16.2)	0.0274
Cough severity, VAS, mm	63.2±20.1	61.1±23. 0	−18.8 (−25.5 to −12.0)	−12.4 (−19.2 to −5.5)	–6.4 (−14.8 to 2.0)	0.1334

EQ-5D-5L: EuroQol Questionnaire-5 Dimensions-5 Levels; EQ-VAS: EuroQol visual analogue scale; LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale.
[#]Japanese version.

TABLE 4 Treatment-emergent adverse events

	Sivopixant (N=31)		Placebo (N=31)	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Patients with any TEAE	11 (35.5)	17	9 (29.0)	14
Dermatitis contact	3 (9.7)	4	1 (3.2)	1
Nasopharyngitis	1 (3.2)	1	0	0
Dizziness	1 (3.2)	1	0	0
Dysgeusia	1 (3.2)	1	0	0
Hypogeusia	1 (3.2)	1	0	0
Rhinitis allergic	1 (3.2)	1	0	0
Abdominal pain upper	1 (3.2)	1	0	0
Drug-induced liver injury	1 (3.2)	1	0	0
Erythema	1 (3.2)	1	0	0
Osteoarthritis	1 (3.2)	1	0	0
Chest discomfort	1 (3.2)	1	0	0
Dysphonia	1 (3.2)	1	1 (3.2)	1
Hypoesthesia oral	1 (3.2)	1	1 (3.2)	1
Gastroenteritis	0	0	1 (3.2)	1
Influenza	0	0	1 (3.2)	1
Tension headache	0	0	1 (3.2)	1
Vertigo positional	0	0	1 (3.2)	1

Oedema mouth	0	0	1 (3.2)	1
Oral pain	0	0	1 (3.2)	1
Erythema annulare	0	0	1 (3.2)	1
Bursitis	0	0	1 (3.2)	1
Post-traumatic neck syndrome	0	0	1 (3.2)	1
Asthma	1 (3.2)	1	2 (6.5)	2

TEAE: treatment-emergent adverse event.

TABLE 5 Treatment-related adverse events

	Sivopixant (N=31)		Placebo (N=31)	
	Number of patients (%)	Number of events	Number of patients (%)	Number of events
Patients with any treatment-related AEs	4 (12.9)	4	1 (3.2)	1
Nervous system disorders	2 (6.5)	2	0	0
Dysgeusia	1 (3.2)	1	0	0
Hypogeusia	1 (3.2)	1	0	0
Gastrointestinal disorders	1 (3.2)	1	1 (3.2)	1
Hypoesthesia oral	1 (3.2)	1	1 (3.2)	1
Hepatobiliary disorders	1 (3.2)	1	0	0
Drug-induced liver injury	1 (3.2)	1	0	0

Treatment-related AEs are defined as events in which causality cannot be denied among AEs reported after initial administration of study drugs.

AE: adverse event.

Supplementary Material

Randomised trial of the P2X$_3$ receptor antagonist sivopixant for refractory chronic cough

Akio Niimi, Junpei Saito, Tadashi Kamei, Masaharu Shinkai, Hiroyuki Ishihara, Mitsuaki Machida and Sayaka Miyazaki

Supplementary Methods

Study ethics

The protocol, informed consent form and Investigator's Brochure were submitted to an institutional review board by the investigator at each study site and reviewed and approved by the institutional review board before the study was initiated. The study was conducted in accordance with the consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical guidelines, applicable International Council for Harmonisation Good Clinical Practice guidelines, and other applicable laws and regulations.

Participants

Patients with insufficient improvement in cough symptoms after treatment for diseases considered to be causing the cough were enrolled as RCC patients, and patients whose disease causing the cough was unidentifiable by a variety of inspections and inquires or was unknown, were enrolled as UCC patients [E1]. The investigators that participated in this study were mostly cough specialists. The investigators confirmed patients were RCC or UCC using the appropriate tests and enrolled the patients using the above definitions.

Patients had to have a subjective cough severity assessment using a visual analogue scale (VAS) of ≥40 mm and an average subjective cough frequency while awake of ≥10 times per hour during the past 24 hours for ≥70% of the days during the screening period (1–4 weeks), as recorded in a patient diary.

The following patients were excluded: (1) current smokers or former smokers who had either ceased smoking within the past 6 months or had a smoking history of ≥20 pack-years; (2) patients taking angiotensin-converting enzyme inhibitors or with a history of angiotensin-converting enzyme inhibitor therapy within 3 months before screening; (3) patients with a marked finding on a chest X-ray or chest computed tomography (CT) scan suggestive of a possible cause of chronic cough within 1 year before the screening visit (but after the onset of chronic cough), or judged by the investigator or subinvestigator to be ineligible to participate owing to lung disease, or absence of a chest X-ray or chest CT scan within 1 year before the screening visit; (4) patients with a pre-bronchodilator forced expiratory volume in 1 second/forced vital capacity <60% at the screening visit; (5) patients with an infection in the upper or lower respiratory tract, or significant changes in lung function or condition within 4 weeks before the screening visit or during the screening visit to the day before the first administration day; (6) patients with mucous hypersecretion in the respiratory tract whereby cough would be induced; or (7) patients who had started treatment with a macrolide antibiotic or proton pump inhibitor for cough treatment within 12 weeks of the day before the first administration day, had received bronchial thermoplasty, or had started using a biological drug for asthma within 4 months of the day before the first administration day. Patients were prohibited from using the following treatments between the day before the first administration day of the study drugs and the end of the second treatment period (or the time of discontinuation): drugs with an antitussive action (*e.g.* opioids, codeine, codeine phosphate, dextromethorphan, and their combination drugs); herbal medicines with an antitussive action; drugs with an expectorant action; angiotensin-converting

enzyme inhibitors; muscle relaxants; pregabalin, gabapentine, and tricyclic antidepressants; anaesthetics (except for temporal local anaesthetics); adrenal corticosteroids (except for topical products and those permitted); cyclosporin; erythromycin; itraconazole; methotrexate; salazosulfapyridine; rosuvastatin calcium, atorvastatin calcium hydrate; apixaban, rivaroxaban, dabigatran etexilate methanesulfonate, edoxaban; ticagrelor; riociguat; aliskiren fumarate; colchicine; fentanyl, fentanyl citrate; loperamide hydrochloride; digoxin, methyl digoxin; mirabegron; tolvaptan; other investigational drugs; and non-drug therapies for cough relief.

Patients were permitted to continue the following treatments if they had been used for ≥2 weeks prior to the day before the first administration day of the study drugs: sleep-inducing drugs; oral and inhaled steroids; bronchodilators (however, on-demand use of a short-acting β_2-agonist was prohibited until the end of the observation related to efficacy evaluation and while patients were wearing a cough monitor); prokinetic drugs; histamine H_2 receptor antagonists; and anti-allergics (histamine H_1 receptor antagonists, leukotriene receptor antagonists, thromboxane receptor antagonists, Th_2 cytokine blockers, mediator release inhibitors). Patients were permitted to continue macrolides (except for erythromycin) and proton pump inhibitors if these had been used for ≥12 weeks prior to the day before the first administration day of the study drugs. Biological products targeting asthma treatment were permitted if patients had been using them for ≥4 months prior to the day before the first administration day of the study drugs. However, use of these treatments was not permitted if they were newly started, discontinued, or if the dosage and administration were changed after the day before the first administration day of the study drugs.

The enrolled patients were randomly assigned (using randomisation codes listed and controlled in an Interactive Web Response System) to either the sivopixant-first group or the placebo-first group using a 1:1 allocation ratio. Blinding was maintained for all patients until database lock, and the randomisation information was masked to the sponsor, the investigator or subinvestigator and the study centre staff. Unblinding at the request of an investigator was allowed only in the event of an emergency or adverse event (AE) for which it was necessary to know the study treatment to determine an appropriate course of therapy.

The full analysis set (FAS) included all randomised patients who received at least one dose of the study drug and who had cough monitor measurements at baseline and at least one time point after the initiation of study drug administration. Even if there was a prescription error during the study, analyses in this population were performed not by the actual treatment but by the allocated treatment. The per protocol set (PPS) included all randomised patients who were included in the FAS and satisfied none of the following conditions: (1) did not meet protocol inclusion criteria or met protocol exclusion criteria; (2) had insufficient treatment compliance with the study drug; (3) had violations of restrictions on concomitant treatments; and (4) change in number of coughs per hour in the daytime from baseline to 2 weeks after starting drug administration in any treatment period was not obtained. The safety population included all randomised patients who received at least one dose of the study drug. Analyses in this population were performed not by the allocated treatment but by the actual treatment.

Outcome measurements

The objective frequency of cough was measured using data collected from a VitaloJAK™ (Vitalograph, Buckingham, UK) cough monitor device with a chest wall contact sensor (attached to the skin of the chest wall by adhesive tape) and a lapel microphone. Patients were instructed to wear the cough monitor device for 24 hours during the following days: (1) day prior to the first treatment period; (2) last day of the first treatment period; (3) last day of the washout period, prior to the first day of the second treatment period; and (4) last day of the second treatment period. The number of coughs per hour was calculated for the following periods: 24 hours, daytime (07:00–19:59), night-time (20:00–06:59 the next day), while awake and while asleep. The Leicester Cough Questionnaire (LCQ) is a valid, repeatable, 19-item, self-completed, quality-of-life measure of chronic cough, which is responsive to change. The scale assesses three domains (physical, social and psychological) and has been found useful in clinical trials and longitudinal studies [E2]. The Japanese LCQ was translated from the original English version to Japanese using the forward and backward translation method and has been confirmed to have a high internal consistency in line with that of the original version [E3]. The mean cough severity by VAS was assessed by the patient using a scale from 0 mm (no cough) to 100 mm (the worst cough).

The safety endpoints were the occurrence of AEs and treatment-related AEs and other safety findings, including blood pressure, pulse rate, electrocardiogram and other clinical laboratory tests. AEs were classified by System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities Version 21.0, except where otherwise noted. Treatment-emergent AEs (TEAEs), defined as AEs reported after the

initial dose of study drug, were used for safety analyses. TEAEs reported before the

initial administration in the second treatment period were associated with the study drug

received in the first treatment period, and TEAEs reported on or after the initial

administration in the second treatment period were associated with the study drug

received in the second treatment period. The number and proportion of patients who

experienced at least one TEAE were summarised by study drug. The number of events

reported was calculated. TEAEs with an outcome of death, serious TEAEs other than

death, TEAEs leading to discontinuation of the study drug and treatment-related AEs

were summarised in the same manner.

Statistical analysis

In the mixed-effects model of the primary outcome evaluation, the study drug, treatment

sequence group (sivopixant-first group and placebo-first group) and treatment period

were considered fixed effects, the patient as random effect and the common logarithm

of the frequency of coughs per hour in the daytime at baseline as covariate. The

secondary efficacy outcomes, adjusted by placebo, were assessed by applying a

mixed-effect model to the difference from baseline after administration of sivopixant for

2 weeks in each treatment period as a response. Efficacy outcomes were evaluated for

the FAS and the PPS.

References

E1. Gibson P, Wang G, McGarvey L, *et al.* Treatment of unexplained chronic cough: CHEST guideline and expert panel report. *Chest* 2016; 149: 27-44.

E2. Birring SS, Prudon B, Carr AJ, *et al.* Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; 58: 339–343.

E3. Kanemitsu Y, Niimi A, Matsumoto H, *et al.* Gastroesophageal dysmotility is associated with the impairment of cough-specific quality of life in patients with cough variant asthma. *Allergol Int* 2016; 65: 320–326.

Supplemental Table

TABLE S1 Prior drugs used for cough treatment (≥3 patients in the safety population)

Drug name	Total (N=31)
Montelukast sodium	8 (25.8)
Tiotropium bromide	8 (25.8)
Fluticasone propionate; formoterol fumarate	7 (22.6)
Theophylline	5 (16.1)
Budesonide; formoterol fumarate	5 (16.1)
Salbutamol sulfate	4 (12.9)
Ambroxol hydrochloride	4 (12.9)
Lansoprazole	4 (12.9)
Ciclesonide	4 (12.9)
Fluticasone furoate; vilanterol trifenatate	4 (12.9)
Aminophylline	3 (9.7)
Prednisolone	3 (9.7)
Mecobalamin	3 (9.7)
Carbocisteine	3 (9.7)
Procaterol hydrochloride	3 (9.7)
Olopatadine hydrochloride	3 (9.7)
Bilastine	3 (9.7)
Bakumondoto[#]	3 (9.7)

Data are presented as n (%). Some patients may have more than one prior drug.

[#]A herbal medicine.

TABLE S2 Number of coughs per hour at baseline and day 15 of each treatment period

Period	Treatment period	Time point	Sivopixant - first, Placebo - second (n=16)	Placebo - first, Sivopixant - second (n=15)
Daytime	1st treatment	Baseline	53.4 (64.2)	59.1 (38.0)
		Day 15	28.9 (50.0)	40.8 (44.6)
	2nd treatment	Baseline	30.4 (43.6)	36.6 (33.0)
		Day 15	29.5 (48.5)	15.2 (12.3)
Night-time	1st treatment	Baseline	19.9 (26.5)	28.1 (21.6)
		Day 15	18.0 (34.9)	15.7 (13.0)
	2nd treatment	Baseline	10.3 (17.0)	16.8 (18.1)
		Day 15	11.9 (23.1)	6.2 (6.1)
24 hours	1st treatment	Baseline	38.0 (46.2)	44.9 (26.6)
		Day 15	23.9 (42.8)	29.7 (28.7)
	2nd treatment	Baseline	21.1 (31.1)	27.4 (23.1)
		Day 15	21.4 (36.7)	11.3 (8.9)
Awake	1st treatment	Baseline	56.8 (79.1)	60.5 (37.6)
		Day 15	36.5 (74.3)	41.2 (38.6)
	2nd treatment	Baseline	33.6 (60.6)	36.7 (31.1)
		Day 15	32.1 (61.1)	15.9 (13.0)
Asleep	1st treatment	Baseline	4.5 (5.2)	5.2 (10.4)
		Day 15	3.2 (4.4)	4.4 (7.8)
	2nd treatment	Baseline	1.7 (3.1)	5.3 (10.3)
		Day 15	2.5 (2.9)	1.9 (2.6)
LCQ	1st treatment	Baseline	11.9 (3.9)	10.8 (3.7)
		Day 15	14.7 (3.7)	12.7 (3.3)

2nd treatment	Baseline	14.2 (4.2)	12.3 (3.7)
	Day 15	14.2 (4.4)	14.5 (2.8)

Data are presented as the mean (SD).
LCQ: Leicester Cough Questionnaire.