Randomised trial of the $P2X_3$ receptor antagonist sivopixant for refractory chronic cough

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Shareable abstract (@ERSpublications)
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. https://bit.ly/3awojQH

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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 of treatment, the placebo-adjusted ratios of the average hourly number of coughs to baseline during daytime (primary end-point) and over 24 h (secondary end-point) 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 >8 weeks, affects ∼10% of the general population worldwide, 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 (UCC) [4, 5]. Most cases of refractory chronic cough or UCC (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 (Aδ 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. Patients had a cough severity assessment using a visual analogue scale (VAS) of ⩾40 mm and an average subjective cough frequency while awake of ⩾10 h^{-1} during the previous 24 h 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 the 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 end-point was the ratio of the average number of coughs per hour in the daytime after 2 weeks of administration of sivopixant to that of baseline. The secondary efficacy end-points were: the

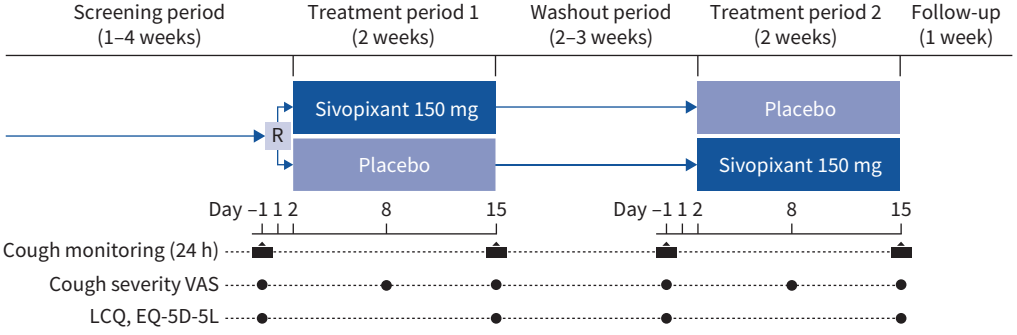

FIGURE 1 Study design. Day 1 is the day immediately after day −1. R: randomised on day 1; VAS: visual analogue scale; LCQ: Leicester Cough Questionnaire (Japanese version); EQ-5D-5L: EuroQol Questionnaire-5 Dimensions-5 Levels (Japanese version).

ratio of the average number of coughs per hour in 24 h, during night-time, while awake and while asleep after 2 weeks of 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 LCQ total score (1.3 points) [19] was evaluated.

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

Statistical analysis

Continuous data were presented as mean with standard deviation, whereas categorical data were presented as count and frequency. The primary outcome, adjusted by placebo, was evaluated by applying a mixed effects 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 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) or 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 $kg \cdot m^{-2}$. The most common underlying disorders in all 31 patients were asthma (45%), cough variant asthma (32%), rhinitis (19%) and gastro-oesophageal reflux disease (16%) (some patients had two or more underlying disorders). Cough was unexplained in 19% of patients. 21 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 (supplementary table S1). The mean±SD duration of cough was 97.6±102.3 months. The mean±SD forced expiratory volume in 1 s/forced vital capacity ratio 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 of administration of the study drug to that of baseline (primary end-point) 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 of sivopixant administration to that of baseline was −31.6% (95% CI −53.6–0.8%; p=0.0546) (table 2). The individual patient data are shown in figure 3. Statistical analysis showed that order effects (p=0.8863) and period effects (p=0.7238) were not observed, and the number of coughs decreased in the sivopixant group during the second treatment period. However, the mean number of coughs per hour in the daytime at baseline in the second treatment period (30.4 in the sivopixant-first group and 36.6 in the placebo-first group) was lower than the number at baseline in the first treatment period (53.4 in the sivopixant-first group and 59.1 in the placebo-first group) and did not return to the baseline levels of the first treatment period (supplementary table S2).

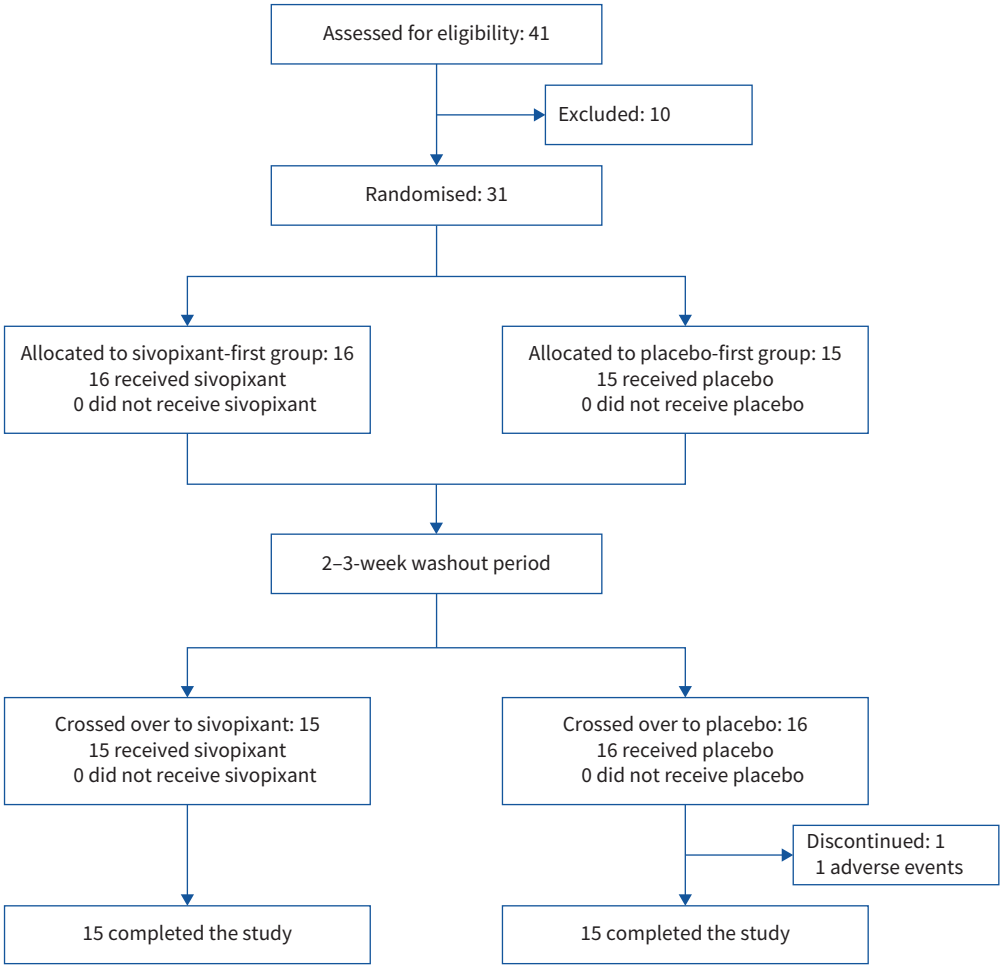

FIGURE 2 Patient flowchart.

The ratio of the average number of coughs per hour in the 24 h after 2 weeks of 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 the 24 h after 2 weeks of sivopixant administration to that of baseline was −30.9% (95% CI −51.3–−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 of 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 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 and figure 3). The proportion of patients who had an increase in LCQ total 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 −14.8–2.0 mm; p=0.1334).

For EQ-5D-5L score, the change from baseline after 2 weeks of 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 of 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

TABLE 1 Baseline characteristics of included patients

	Sivopixant-first group (n=16)	Placebo-first group (n=15)	Total (n=31)
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)
Gastro-oesophageal 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)
Sino-bronchial 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 n (%) or mean±SD, unless otherwise stated. FEV_1: forced expiratory volume in 1 s; 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".

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 of 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 of sivopixant administration to that of baseline was −27.7% (95% CI −52.6–10.4%; p=0.1263).

Safety

The safety analysis population included all 31 randomised patients. Treatment-emergent AEs occurred in 35.5% (11 out of 31) of patients during sivopixant administration and in 29.0% (nine out of 31) during placebo administration (table 4). One patient had two treatment-emergent AEs (tension headache and positional vertigo) leading to discontinuation of the study drug during placebo administration. All treatment-emergent AEs 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

TABLE 2 Changes in cough frequency (full analysis set)

	Baseline cough frequency, h^{-1} (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–−36.8)	−33.0 (−51.6–−7.2)	−31.6 (−53.6–0.8)	0.0546
24 h	20.0 (13.7–29.3)	18.9 (11.9–30.2)	−52.6 (−64.7–−36.3)	−31.4 (−49.1–−7.4)	−30.9 (−51.3–−2.1)	0.0386
Night-time	8.8 (5.3–14.7)	9.5 (5.7–15.8)	−45.2 (−60.7–−23.5)	−22.7 (−44.8–8.4)	−29.1 (−53.6–8.3)	0.1074
Awake	27.3 (18.5–40.3)	26.2 (16.5–41.5)	−50.5 (−63.1–−33.5)	−33.3 (−50.5–−10.0)	−25.8 (−48.3–6.5)	0.1022
Asleep	2.5 (1.4–4.7)	1.6 (0.8–3.3)	−14.8 (−48.3–40.6)	7.9 (−35.1–79.6)	−21.0 (−57.1–45.2)	0.4346

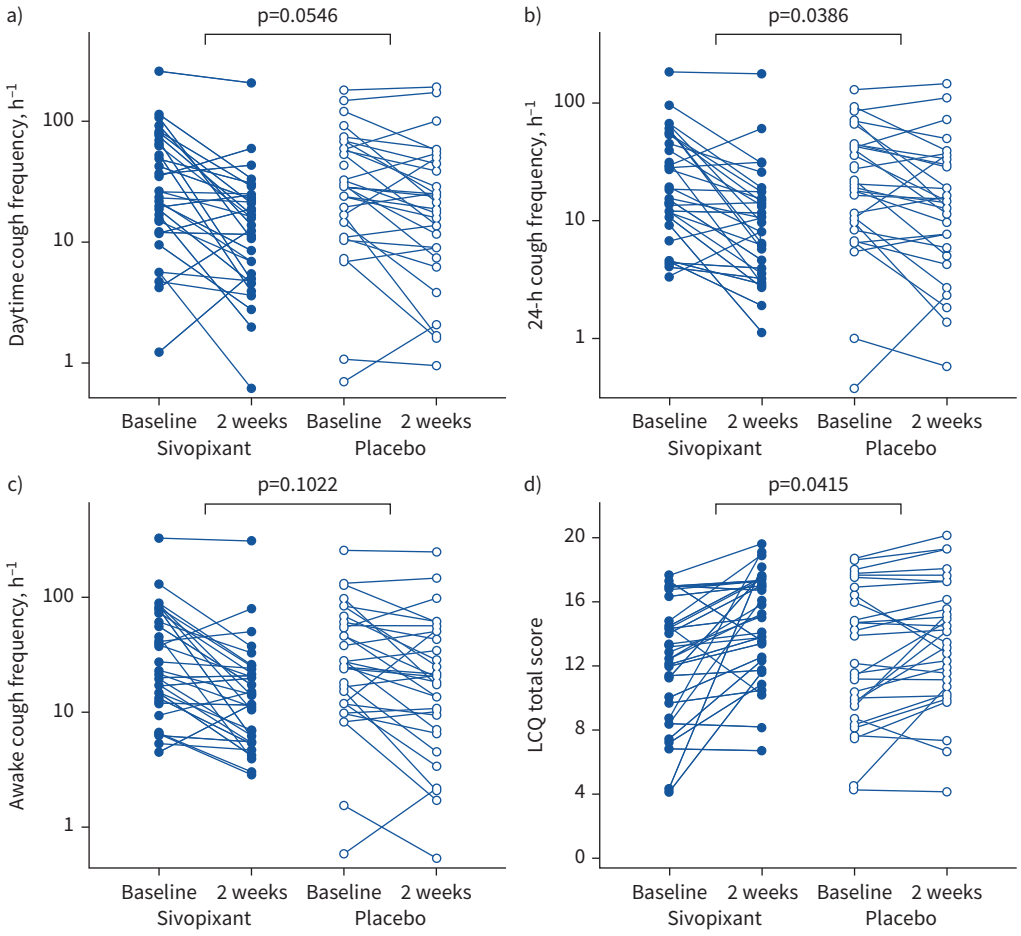

FIGURE 3 Individual plots of cough frequency a) in the daytime, b) over 24 h and c) while awake, and d) Leicester Cough Questionnaire (LCQ; Japanese version) total score. Cough frequency in a–c) is plotted on a common log scale. p-values are for the group-level placebo-adjusted differences between sivopixant and placebo in the change from baseline at 2 weeks (tables 2 and 3).

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% (four out of 31) of patients during sivopixant administration and 3.2% (one out of 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

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±0.1956	0.8166±0.2285	0.10 (0.06–0.15)	0.01 (−0.04–0.06)	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 (−3.1–8.7)	8.6 (1.0–16.2)	0.0274
Cough severity (VAS), mm	63.2±20.1	61.1±23.0	−18.8 (−25.5–−12.0)	−12.4 (−19.2–−5.5)	−6.4 (−14.8–2.0)	0.1334

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

TABLE 4 Treatment-emergent adverse events (AEs)

	Sivopixant (n=31)		Placebo (n=31)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
Patients with any treatment-emergent AEs	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

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 ECG 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.

TABLE 5 Treatment-related adverse events (AEs)

	Sivopixant (n=31)		Placebo (n=31)	
	Patients, n (%)	Events, n	Patients, n (%)	Events, n
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.

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 of sivopixant administration (primary end-point) was greater than after placebo. However, the placebo-adjusted difference was not statistically significant and the primary end-point was not met. In contrast, statistical significance between sivopixant and placebo was observed in the number of coughs per hour over 24 h, and sivopixant improved the subjective LCQ score. Very few mild taste disturbance treatment-emergent AEs 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, 20 and 50 mg resulted in changes in the frequency of awake cough of between −22.0% (95% CI −41.8–4.6%; p=0.097) with 7.5 mg and −37.0% (95% CI −53.3–−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.* [9] showed that, depending on the dose, 10–81% of gefapixant-treated patients reported taste-related AEs (dysgeusia, hypogeusia or ageusia). With a dose of 50 mg, 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 treatment-emergent AEs 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 (two out of 31 (6.5%)). Furthermore, no patient discontinued treatment due to taste-related treatment-emergent AEs.

Low rates of taste-related treatment-emergent AEs 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 study of the other $P2X_3$ selective antagonist (eliapixant) [24].

In this study, the ratio of the number of coughs per hour in 24 h 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 of 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-h period in this study (table 2). However, variability was higher for daytime cough than a 24-h period cough, which might have affected the result. Our results (figure 3) showed that 24-h cough frequency might be the optimum end-point 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 LCQ total 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 ∼30% when patients received placebo in the daytime, over 24 h 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 effects. 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 effects and period effects were not observed, which suggests a low probability for carryover effects. 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 nonasthmatic chronic cough, is characterised by a 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 (ClinicalTrials.gov: NCT04110054).

In conclusion, although the results of this phase 2 study should be viewed with caution as the primary end-point 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/ethnicities and countries.

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This study was prospectively registered with the Japan Pharmaceutical Information Center Clinical Trials Information database with identifier JapicCTI-184027. Data from this study may be available on reasonable request by healthcare providers, investigators and researchers to address specific scientific or clinical objectives. Shionogi & Co., Ltd is committed to reviewing requests from researchers for access to clinical trial protocols, de-identified patient-level clinical trial data and study-level clinical trial data. See more at: www.shionogi.com/global/en/company/policies/clinical-trial-data-transparency-policy.html

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