A double-blind randomised placebo-controlled trial investigating the effects of lesogaberan on the objective cough frequency and capsaicin-evoked coughs in patients with refractory chronic cough

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Lesogaberan, a peripherally acting $GABA_B$ agonist, does not reduce 24-h cough frequency in patients with chronic cough despite significantly reducing capsaicin-induced coughing https://bit.ly/3uGyPQL

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Abstract

Objective Baclofen is a centrally acting γ-aminobutyric acid type B ($GABA_B$) receptor agonist which reduces gastro-oesophageal reflux and suppresses the cough reflex; however, central nervous system side-effects limit its use. Lesogaberan is a novel peripherally acting $GABA_B$ agonist, but its effects on refractory chronic cough are unknown.

Design We performed a single-centre, placebo-controlled, double-blind randomised crossover study in patients with chronic cough, refractory to the treatment of underlying conditions. Patients were randomised to treatment with lesogaberan 120 mg modified release twice daily or matched placebo for 2 weeks and then crossed over to the alternative therapy after a 2-week washout. The primary end-point was 24-h cough frequency measured with an acoustic monitoring system. In addition, cough responses to capsaicin were measured, and gastro-oesophageal reflux assessed by 24-h pH/impedance at screening.

Results 22 patients were randomised to receive lesogaberan/placebo or placebo/lesogaberan (female (73%); mean±SD age 63.7±7.2 years; median (interquartile range) cough duration 10.5 (5.8–17.0) years; mean (95% CI) 45 (29–67) reflux events in 24 h; two patients had abnormal oesophageal acid exposure times). Although lesogaberan reduced cough counts by 26% over placebo, this did not reach statistical significance (p=0.12). However, lesogaberan did significantly improve cough responses to capsaicin (p=0.04) and the number of cough bouts (p=0.04) compared with placebo. Lesogaberan was well tolerated in this study.

Conclusions Lesogaberan improved cough hypersensitivity and the number of bouts of coughing, but not coughs per hour. This implies a possible role for peripheral $GABA_B$ receptors in refractory chronic cough.

Introduction

Cough is the commonest presenting symptom in primary care consultations and an estimated 10% of adults worldwide suffer from a cough lasting >8 weeks, *i.e.* chronic cough [1, 2]. Patients presenting with chronic

coughing are typically female, aged 50–70 years and report coughing on exposure to usually innocuous triggers such as changes in temperature, irritant aerosols such as cleaning produces and use of their voice [3]. They also have heightened responses to inhaled irritants known to activate airway nerves [4]. Current management strategies focus on treating potential comorbidities such as asthma, nasal disease and gastro-oesophageal disease, which may improve coughing, but in some patients chronic coughing is refractory to treatment of associated comorbidities, or comorbidities cannot be identified, known as refractory chronic cough (RCC). At present there are no effective licensed therapies for patients with RCC.

Many studies report that gastro-oesophageal reflux disease (GORD) is commonly associated with chronic coughing. However, randomised controlled trials of antacid therapy in chronic cough patients have largely produced negative findings [5, 6], which has led to current cough consensus guidelines discouraging the routine prescribing of acid suppression therapy [7]. The role of GORD in RCC is unclear. Various mechanisms have been suggested, including microaspiration of refluxate, weakly/nonacid reflux and laryngopharyngeal reflux provoking coughing, but little evidence is available. However, there is evidence to suggest temporal associations between reflux and cough events in patients with chronic cough, suggesting that reflux events may be capable of triggering coughing irrespective of their acidity [8–10]. The oesophagus and the bronchial tree are both vagally innervated and share the same embryonic origins; thus, reflux episodes, even those confined to the oesophagus, may provoke coughing through neuronal crosstalk. Therefore, therapies that reduce all reflux events (regardless of acidity) may have the greatest potential to be effective in patients with cough driven by reflux.

γ-Aminobutyric acid B ($GABA_B$) receptor agonists such as baclofen have been shown to reduce cough evoked experimentally by inhaling capsaicin, and therefore been proposed as a potential antitussive therapy [11, 12]. GABA is the main inhibitory neurotransmitter in the nervous system and $GABA_B$ receptors are widely distributed in the body, including the airways and the lower oesophageal sphincter. In addition, baclofen has been shown to reduce the frequency of transient lower oesophageal relaxations (TLOSR), the main mechanism mediating reflux events in GORD [13–15]. However, baclofen is associated with central nervous system (CNS) side-effects such as drowsiness and even seizures, limiting its use in clinical practice.

Lesogaberan is a novel peripherally acting $GABA_B$ receptor agonist devoid of CNS side-effects, as it is actively transported out of the CNS. Lesogaberan was developed as an add-on treatment to proton-pump inhibitors in patients with GORD. In initial trials, lesogaberan significantly reduced TLOSRs [16, 17], but was only marginally superior to placebo in achieving an improvement in typical symptoms of reflux disease [18]. However, patient selection for these studies has been questioned [19]. Unlike baclofen, lesogaberan does not appear to supress capsaicin-evoked cough in healthy controls, but this may not exclude an effect on the hypersensitised cough reflex responses exhibited by patients with RCC [20, 21].

We hypothesised that lesogaberan may be effective at reducing cough in RCC patients *via* two possible mechanisms: by reducing TLOSRs and by reducing the sensitivity of the cough reflex. We therefore performed a study investigating the effects lesogaberan on spontaneous cough frequency and capsaicin-evoked cough responses in patients with RCC. In addition, we explored whether patients with significant reflux-cough associations were more likely to benefit from lesogaberan.

Methods

The study was performed in accordance with the Declaration of Helsinki, good clinical practice and applicable regulatory requirements including local ethics board approval (Liverpool East, REC reference: 14/NW/1497).

Study subjects

Adults (aged >18 years) with RCC (>8 weeks' duration) attending a specialist cough clinic (between 23 July 2015 and 10 September 2017) were recruited. All patients had previously undergone assessment and treatment trials to exclude other causes of RCC and manage any triggers, as per current guidelines [22]. We did not select patients on the basis of typical GORD symptoms, as these should be treated with standard therapies. Current smokers (<6 months' abstinence) and ex-smokers with >20 pack-years' history were excluded. Patients who had a respiratory tract infection or other significant illness within a 4-week period prior to starting the study were also excluded. Patients with significantly abnormal lung function (forced expiratory volume in 1 s/forced vital capacity ratio <70%) or chest radiology were excluded. Patients taking ACE inhibitors or currently taking drugs thought to affect cough reflex sensitivity (opiates, pregabalin or gabapentin) were also excluded.

Study design

This was a single-centre, double-blind randomised, placebo-controlled, crossover study, comparing 2 weeks' treatment with lesogaberan (120 mg modified release (MR) twice daily) *versus* placebo in RCC patients. At screening, patients underwent high-resolution impedance manometry (HRIM) followed by simultaneous 24-h cough and pH/impedance monitoring. Patients were then randomised to lesogaberan 120 mg MR twice daily or matched placebo for 2 weeks followed by a 7–14-day washout period and then crossed over to the alternative therapy. For each treatment period, we measured capsaicin cough challenge and 24-h cough frequency at baseline (pre-treatment) and on day 14 of therapy. Capsaicin cough challenge was performed at 2 h post-dose (corresponding to the maxiumum concentration) on day 14. Leicester Cough Questionnaire (LCQ), Reflux Symptom Questionnaire 7-day recall (RESQ-7) and visual analogue scores (VAS) were completed at the same time points.

Cough measurements

Cough frequency

Participants underwent 24-h ambulatory acoustic cough monitoring using the VitaloJAK cough monitor (Vitalograph, Buckingham, UK). Cough sounds per hour were quantified by a semi-automated method using validated custom-written software [23–25]. Cough "bouts", defined as continuous coughing without a 2-s pause were analysed to permit evaluation of reflux–cough associations [8, 26]. Awake and night-time coughs were analysed as secondary outcomes.

Capsaicin-evoked cough responses

Participants inhaled four breaths of doubling concentrations of capsaicin (to total lung capacity, 0.97–1000 µM; Stockport Pharmaceuticals, Stockport, UK) at 30-s intervals using a dosimeter (KoKo dosimeter; DeVilbiss Healthcare, Somerset, PA, USA) from a nebuliser pot with flow limitation. Coughs evoked in the first 15 s following each inhalation were counted. The challenge continued until the maximum tolerated dose, or the final concentration was inhaled. The maximum number of coughs evoked at any concentration of capsaicin (E_{max}) and the concentration evoking 50% of the maximal response (ED_{50}) were noted.

Patient-reported cough measures

Cough-specific quality of life was assessed using the LCQ [27]. Cough severity was rated by the patients using a 100-mm VAS.

Oesophageal studies

All patients underwent HRIM (Sandhill Scientific, Highland Ranch, CO, USA) and analysed according to the Chicago classification (version 3.0) [28]. HRIM was carried out to assess oesophageal motility and accurately locate the lower oesophageal sphincter to ensure the correct placement of the pH impedance catheter. 24-h multichannel intraluminal impedance-pH monitoring, using a Sleuth pH/impedance ambulatory system (Sandhill Scientific) was then carried out. The distal pH sensor was placed 5 cm above the lower oesophageal sphincter. Patients underwent simultaneous, synchronised 24-h cough recording using the VitaloJAK ambulatory cough recorder. The purpose of the synchronised 24-h pH impedance and cough frequency measurement was to identify reflux–cough associations and thus analyse cough responses in the context of these associations. The 24-h pH impedance data were manually analysed for reflux episodes using the BioView analysis system (Sandhill Scientific) and then reviewed by an experienced technician. Patients taking proton-pump inhibitors and/or histamine (H_2) antagonists were requested to stop their treatments for 2 weeks prior to the test. Data collected during mealtimes and drinks were excluded from the analysis. Gastro-oesophageal reflux episodes were defined as sequential, orally progressing drops in impedance to <50% of the baseline values in two consecutive channels and propagating in retrograde direction to at least the next impedance segment. Acid and nonacid reflux episodes were analysed.

Symptom association probability

Symptom association probability (SAP) was used to assess the probability of an association between cough bouts and reflux episodes [8]. Each 24-h impedance trace was divided into 2-min segments and each segment was assessed for the presence of reflux and/or cough. All cough bouts were then assessed for reflux occurring in the preceding 2 min. The SAP is calculated assuming that reflux and cough events are linked if they fall within 2 min of one another. Fisher's exact test is used to assess whether the proportion of linked events exceeds that expected by chance alone. A SAP of ⩾95% within an individual patient is assumed to indicate a positive association. A validated, semi-automated, custom-written SAP analysis tool based on the Weusten *et al.* [29] method was used. Other measurements that were calculated were 1) the symptom index, defined as the overall percentage of reflux related cough episodes (calculated by number of reflux-related cough episodes/total number of cough episodes)×100% and 2) the symptom sensitivity

index, which is the defined as the percentage of cough-related reflux episodes (calculated by number of cough-associated reflux episodes/total number of reflux episodes×100) [30].

Patient-reported reflux symptoms

The RESQ-7 was used to assess frequency and intensity of GORD symptoms. This is a validated 13-item questionnaire, with a higher score indicating higher symptom burden [31].

Dose justification

We used a lesogaberan dose of 120 mg MR twice daily for a 2-week period. To date, there are no data to determine the optimal dose of lesogaberan required to reduce or inhibit cough in humans. Therefore, we based our dosing selection on safety data and the assumption that doses effective at inhibiting TLOSRs will probably also be effective at inhibiting cough. In a multiple-dosing study of lesogaberan, MR preparation doses of 60 mg, 120 mg, 180 mg and 240 mg twice daily, for 4 weeks, in 661 patients with persistent GORD were used [18] with no apparent advantage of increasing the dose beyond 120 mg. In addition, there were no serious adverse events at the 120 mg twice daily dose; the proportion of adverse events was similar to placebo (120 mg 39% *versus* placebo 31%), whereas there were cases of altered liver function enzymes at 240 mg [18].

Blinding and randomisation

Randomisation was carried out using a computer-generated scheme by Almac (Craigavon, UK), who were independent of the study site and procedures. Blinded study medication was supplied to the pharmacy where it was dispensed. Unblinding was by way of unblinding scratch cards per treatment.

Patients were randomised to two sequences: lesogaberan/placebo or placebo/lesogaberan. The treatment assigned to a patient was determined by an Almac-generated randomisation scheme (block size=10). Treatment numbers were allocated sequentially as the subjects were enrolled.

Outcomes

The primary outcome was the effect of lesogaberan on objective 24-h cough frequency. Secondary outcomes were efficacy in SAP-positive *versus* SAP-negative patients after 2 weeks' treatment as measured by cough frequency (24-h cough recording), changes in capsaicin-evoked cough responses (E_{max}/ED_{50}) and patient-reported outcomes capturing cough severity and reflux symptoms (VAS, LCQ, RESQ-7). In addition, we explored the effect of lesogaberan on cough bouts.

Sample size

Based upon previous cough frequency data in an unselected group of patients with RCC, with 22 patients this study had 80% power to detect a 43% reduction in cough with lesogaberan over placebo, assuming a standard deviation of log cough frequency of ±0.42. Significance was set at the standard level of $p<0.05$ [32].

Statistical methods

Generalised estimating equation (GEE) models were used to analyse the data (SPSS Statistics version 22; IBM, Armonk, NY, USA). The analysis used all the data from the intention-to-treat population (all randomised patients who took at least one dose of the study drug). For cough frequency end-points (24 h, daytime and night-time cough rates), we calculated percentage change from baseline after natural log transformation of the data (0.1 was added to the entire night-time cough frequency data as they contained zero numbers). The GEE models assessed the influence of treatment, period and sequence adjusting for the period specific baseline. Potential carryover effects were examined by the sequence in the model. The influence of a positive/negative SAP on the treatment response was assessed as a factor in the model. Similar models were used to assess the effect of treatment and SAP status on cough severity VAS, LCQ, capsaicin cough responses and RESQ-7 scores. We estimated the difference between treatments and calculated the percentage difference. Significance was set at $p<0.05$.

Results

Participants

22 patients were recruited (between 23 July 2015 and 10 September 2017); two withdrew after randomisation; and 20 completed the study (figure 1). Patients were predominantly female, middle-aged, with normal lung function, and a median cough duration of 10.5 years. There were no current smokers, most (almost 75%) had never smoked and the rest had minimal smoking history. 10 patients were taking acid-suppression therapy (proton-pump inhibitors and H_2 antagonists) for typical reflux symptoms; of these, eight were able to withhold this therapy for the duration of the trial. SAP data were only available on 19 patients, as three were missing (one failed cough monitor, one failed pH/impedance monitor and one

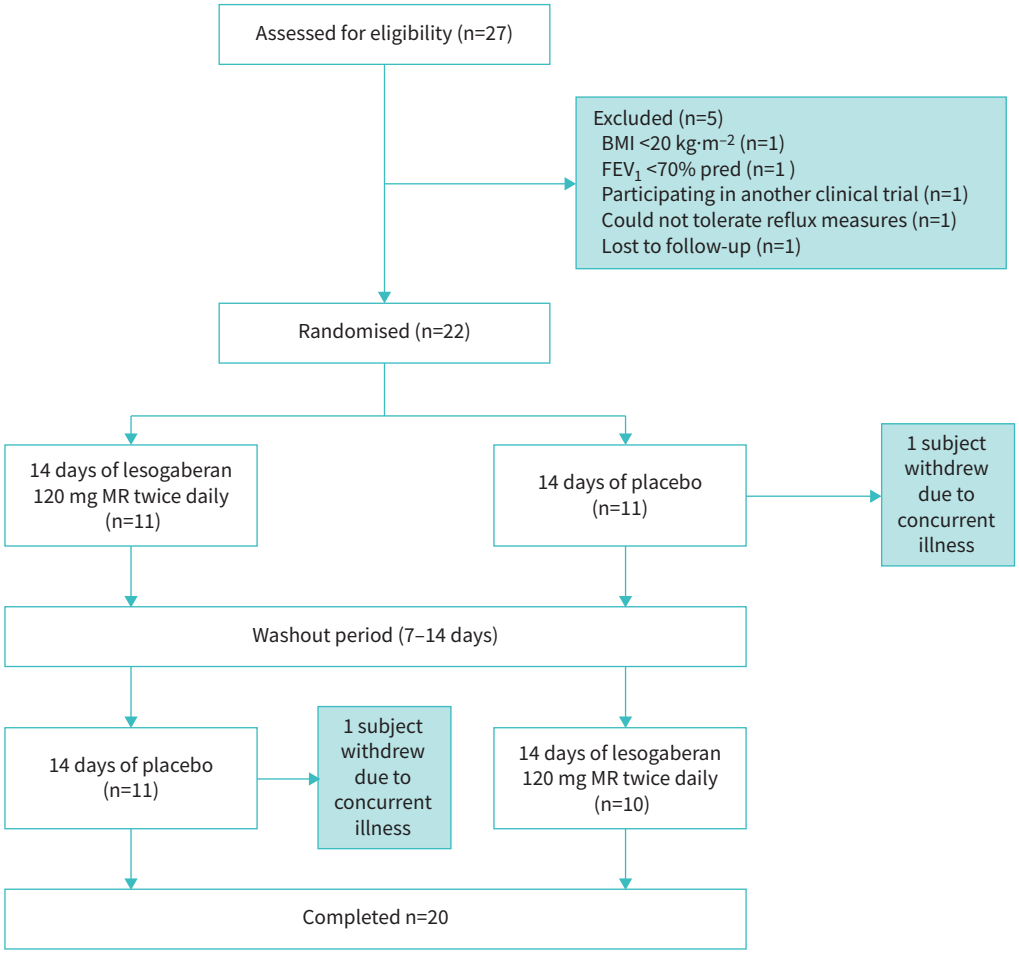

FIGURE 1 Consolidated Standards of Reporting Trials diagram. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; MR: modified release.

had oesophageal studies elsewhere). The mean number of reflux events were within normal limits (<70 events per 24 h), similar to previous studies [8–10] (table 1).

Spontaneous cough frequency

Lesogaberan reduced 24-h cough frequency by 26% compared with placebo. (p=0.12; figure 2 and table 2). SAP category (figure 3) and RESQ-7 (supplementary material) did not significantly predict the response of cough to lesogaberan. Both daytime and night-time cough rates were reduced by lesogaberan compared with placebo, but neither reached statistical significance (p=0.18 and p=0.14, respectively). We explored the effect of lesogaberan on cough bouts, as this method of cough quantification is required for evaluating reflux–cough associations. Lesogaberan reduced 24-h cough bouts by 31% over placebo, p=0.04; figure 2). There were no significant period or sequence effects.

Capsaicin-evoked cough

Only 16 out of 22 patients completed capsaicin cough challenge, due to loss of the supply of capsaicin during the study. Lesogaberan reduced capsaicin-evoked cough compared with placebo (p<0.001). The E_{max} was lower (p=0.02) and the ED_{50} higher (p=0.02) after lesogaberan treatment compared with placebo (figure 4).

Gastro-oesophageal reflux measures

Complete impedance data was available in 19 patients. The mean number of reflux events was 45 (95% CI 29–67) with a median of 83 cough bouts (95% CI 46–191) during the 24-h pH impedance study period, *i.e.* almost double the number of cough bouts compared to reflux events. The symptom index showed that 11.6% (95% CI 8.9–20.2%) of these cough bouts were preceded by reflux within a 2-min window. Even

TABLE 1 Patient demographics

Patients	22
Age, years	63±7.0
Female	16 (73)
Body mass index, kg·m^{-2}	25.8±4.0
Smoking status	
Never-smoker	16 (73)
Ex-smoker	6 (27)
Pack-years	0 (0–2.4)
Cough duration, years	10.5 (5.8–17.0)
FEV$_1$, % predicted	95±14.6
FVC, % predicted	110±20.7
Baseline 24-h coughs, coughs·h^{-1}	24 (12–32)
LCQ score[#]	14.2±3.8
VAS daytime, mm	43±25.6
VAS night-time, mm	17 (8–25)
SAP-positive[¶]	11(58)
Symptom index,[¶] **%**	11.6 (11.5–26.0)
Symptom sensitivity index,[+] **%**	17.3 (11.5–26.0)
Acid exposure time,[¶,§] **%**	2.35 (0.65–3.83)
Total reflux episodes[+]	48.9 (23.5–68.8)
Patients with abnormal reflux events[+]	3 (15)
Ineffective oesophageal motility[+]	8 (40)
LOSP,[+,f] **mmHg**	22.2 (6.7–26.2)

Data are presented as n, mean±SD, n (%) or median (interquartile range). FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; LCQ: Leicester Cough Questionnaire; VAS: visual analogue scale; SAP: symptom association probability; LOSP: lower oesophageal sphincter pressure. [#]: range 3–21; [¶]: n=19; [+]: n=20; [§]: the percentage of a 24-h period where the pH in the oesophagus is <4 (normal value pH 4 for 4% of 24 h); [f]: normal pressure is 26 mmHg.

in the 58% of patients with a positive SAP analysis, the proportion of reflux episodes associated with cough bouts (the symptom sensitivity index) was only 17.3% (95% CI 11.5–26.0%), therefore the potential efficacy of blocking reflux events with lesogaberan in this study was highly limited by the low number of cough episodes temporally linked to reflux. Only two out of the 19 patients with complete impedance data had a pathological acid exposure time (*i.e.* a pH of <4 for >4% of the 24-h period); therefore, the influence of this on the effect of lesogaberan was not explored.

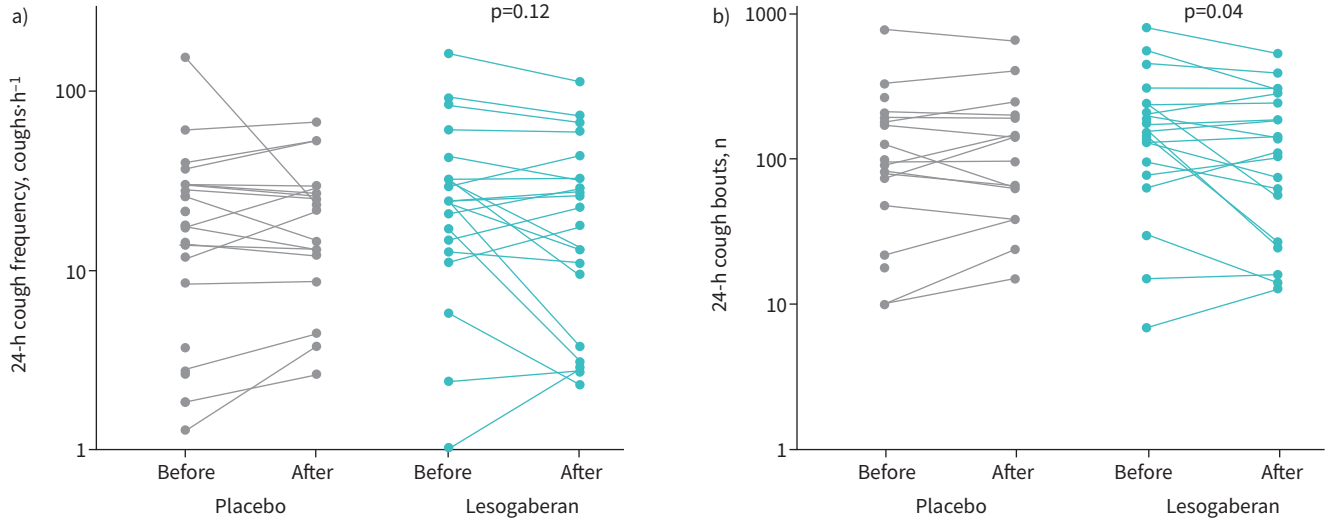

FIGURE 2 a) Cough frequency and b) cough bout data before and after 2 weeks' placebo and lesogaberan treatment. Lesogaberan reduced 24-h cough frequency by 26% (p=0.12) and cough bouts by 31% over placebo (p=0.04).

TABLE 2 Outcomes

	Lesogaberan		Placebo		Difference	p-value
	Week 0	Week 2	Week 0	Week 2		
24-h cough frequency, coughs·h^{-1}	24.6 (13.8–38.0) n=21	22.7 (6.7–38.8) n=21	19.5 (11.1–32.3) n=22	22.6 (11.4–29.2) n=18	−26.1%	0.12
Daytime cough frequency, coughs·h^{-1}	34.7 (17.0–58.9) n=21	28.3 (8.9–55.0) n=21	28.8 (15.1–48.0) n=22	34.6 (14.7–42.5) n=18	−23.1%	0.18
Night-time cough frequency, coughs·h^{-1}	2.5 (0.7–7.1) n=21	1.3 (0.1–9.6) n=21	1.8 (0.2–5.0) n=22	1.02 (0.4–1.9) n=18	−28.1%	0.41
VAS daytime, mm	53.5 (19.8–61.3) n=18	31.5 (22.4–61.9) n=18	45.5 (22.3–65.5) n=20	35.5(18.3–63.5) n=20	−3.1 (−12.1–5.92)	0.50
VAS night-time, mm	16.0 (6.5–46.0) n=18	12.0 (0.9–38.1) n=18	17.5 (2.5–28.6) n=20	14.5 (2.0–36.3) n=20	1.0 (−5.8–7.8)	0.768
LCQ	14.0±3.5 n=21	14.9±3.0 n=21	14.7±3.8 n=21	14.7±3.5 n=20	+0.4 (−0.5–1.3)	0.36
E_{max}	25.5 (14.5–40.3)	26.5 (15.3–33.8)	23 (14.3–34)	28 (17.5–46.8)		0.02
ED_{50}	0.89 (−0.1–0.8)	1.19 (0.59–2.10)	1.19 (0.29–1.80)	1.04 (0.37–1.72)		0.02

Data are presented as median (interqartile range), mean±SD or n, unless otherwise stated. Statistical significance p<0.05. VAS: visual analogue scale; LCQ: Leister Cough Questionnaire; E_{max}: maximum number of coughs evoked at any concentration of capsaicin; ED_{50}: concentration evoking 50% of the maximal response.

Patient-reported outcomes

Lesogaberan treatment had no effect on the LCQ (+0.4, 95% CI −0.5–1.3; p=0.36), daytime cough severity VAS or the RESQ-7 (table 2 and supplementary material).

Treatment-emergent adverse events

Lesogaberan 120 mg MR twice daily was well tolerated by the vast majority of patients (table 3). There were no serious adverse events; in particular there were no significant changes in liver function tests (table 3).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of a peripherally acting $GABA_B$ receptor agonist in a group of patients with RCC. Lesogaberan reduced spontaneous cough frequency by 26% over placebo, but this reduction did not reach statistical significance. Similarly, the patient-reported outcomes did not suggest a significant benefit from lesogaberan in cough or reflux symptoms. Interestingly, lesogaberan did reduce capsaicin-evoked cough responses, and exploratory

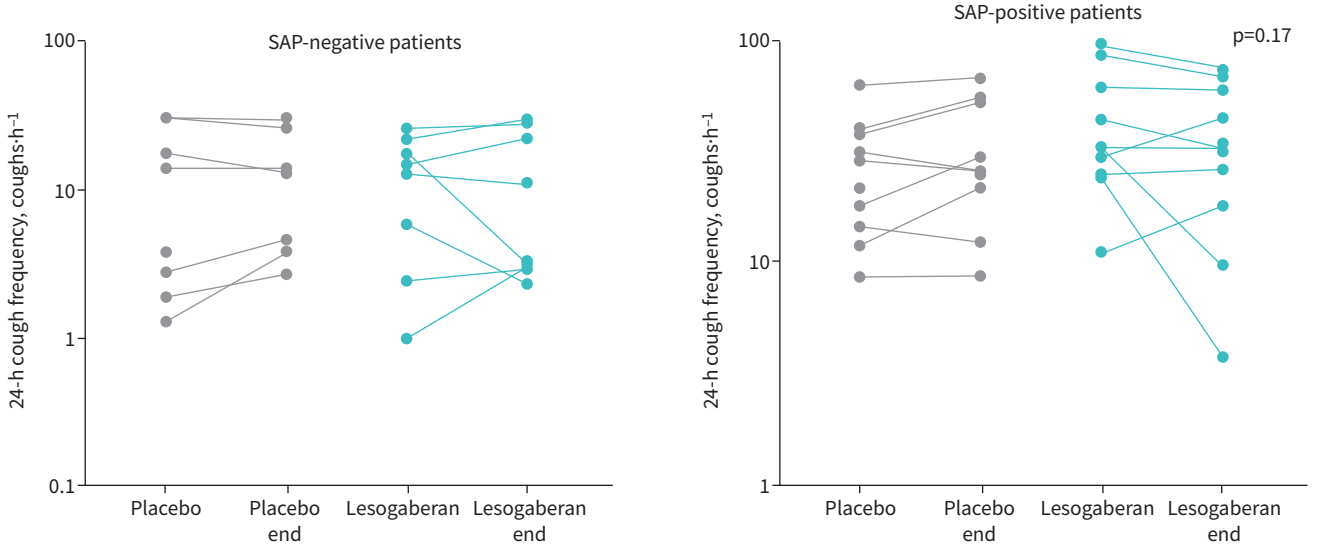

FIGURE 3 Reflux as a predictor of lesogaberan effect on 24-h cough counts. SAP: symptom association probability.

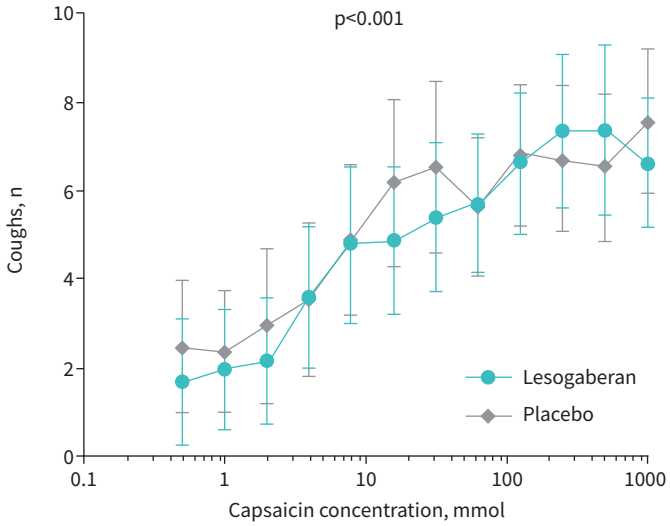

FIGURE 4 Capsaicin-evoked coughs in chronic cough patients after 2 weeks' treatment with placebo *versus* lesogaberan.

analysis suggested that bouts of coughing were significantly reduced by 31% after lesogaberan over the effects of placebo.

The association between RCC and GORD has long been described. Pooled data from trials of acid suppressing therapy suggest that patients with symptoms of heartburn and/or abnormal oesophageal acid exposure accompanying their RCC are most likely to gain benefit from acid-suppressing therapies [6]. The role of nonacid reflux (whether liquid or gaseous) remains controversial and is challenging to investigate in the absence of effective therapies. We used an unlicensed therapy, lesogaberan, to inhibit TLOSRs and thus reflux events (irrespective of acidity or nature) in this patient group and evaluated the effects on

TABLE 3 Treatment-emergent adverse events

	Lesogaberan (n=21)	Placebo (n=22)
Headache	1 (4.8)	4 (18.2)
Worsening cough	3 (14.3)	2 (9.1)
Diarrhoea	3 (14.3)	1 (4.5)
Heartburn	2 (9.5)	1 (4.5)
Back pain	2 (9.5)	1 (4.5)
Constipation	0	2 (9.1)
Light-headed	2 (9.5)	1 (4.5)
Cold-like symptoms/LRTI	0	2 (9.1)
Nausea	1 (4.8)	1 (4.5)
Rhinorrhoea/runny nose	2 (9.5)	0
Sore throat	1 (4.8)	1 (4.5)
Vomiting	2 (9.5)	0
Deranged urea and creatinine	1 (4.8)	0
Haematuria	1 (4.8)	0
Haemoptysis	0	1 (4.5)
Insomnia	0	1 (4.5)
Loss of appetite	0	1 (4.5)
Low capillary blood glucose	1 (4.8)	0
Nosebleed	0	1 (4.5)
Right eyelid soreness	1 (4.8)	0
Urinary frequency	0	1 (4.5)
Skin rash	0	1 (4.5)

Data are presented as n (%). LRTI: lower respiratory tract infection.

cough. Compared with our previous study of temporal reflux cough associations in unselected RCC patients [8], this refractory group had fewer reflux events, and a much smaller number of cough events preceded by reflux (11% *versus* 33%); despite this, a similar proportion were SAP-positive [8]. This may have contributed to the negative findings in this study; however, our previous work found that significant reflux–cough associations were independent of the number of reflux events.

In the normal physiological state TLOSRs are under inhibitory control of $GABA_B$. In clinical and pre-clinical studies, lesogaberan reduced the number of TLOSRs by preventing the loss of inhibition of these events [33–35]. In patients with typical reflux and partial improvement in their symptoms with proton-pump inhibitors/H_2 antagonists, there was a clear dose response between lesogaberan therapy and the reduction in reflux episodes, from 30 mg to 240 mg twice daily [17]. At the 120 mg MR dose of lesogaberan there was a reduction in reflux events by 45% (95% CI −35.1– −53.1%) [18]. Even if lesogaberan was highly effective and blocked all reflux events in our participants, a maximum 11% reduction in cough bouts would be expected, as only this small proportion of coughs appeared to be triggered by reflux in this patient group. In fact, the reduction in cough bouts we observed was much greater (31% over placebo), suggesting that an alternative mechanism independent of reflux may be involved.

The effects of lesogaberan on capsaicin-evoked coughs differed from our previous observations in healthy volunteers [36]. In RCC patients, lesogaberan significantly reduced capsaicin-evoked cough, suggesting an inhibition of the cough reflex, whereas there was no effect in healthy controls. RCC patients are known to have heightened cough responses to capsaicin inhalation relative to healthy volunteers [37]. Lesogaberan attenuated this response, suggesting a possible role for peripheral $GABA_B$ receptors in the pathophysiology of RCC. It is possible that the nonsignificant improvements in cough frequency and significant improvements in cough bouts could be a consequence of the inhibition of peripheral nerves. Although the dose of lesogaberan used in this study had comparable effects to higher doses on reflux events, whether this dose was optimal for suppressing cough reflex hypersensitivity is unknown.

This study demonstrated a reduction in cough bouts. Although this is not standard methodology for quantifying coughs, patients with RCC describe attacks of coughing as particularly troublesome [38, 39] and grouping cough events is necessary to allow the relationships between cough and reflux to be analysed. We speculate that the reason for this could be that $GABA_B$ receptors may play a particular role in the triggering of cough bouts but has little influence on the subsequent bout duration.

The main limitation of this study was the sample size, which was insufficient for a 26% reduction in 24-h cough frequency to be statistically significant. *Post hoc* analysis from this study showed that we needed to recruit $\geqslant$70 patients (requiring a multicentre study) to achieve statistical significance. Recent data have estimated that the minimal clinically important difference in objective cough counts in RCC patients is 20–30% [40], suggesting that the improvement in cough frequency in this study could be of clinical relevance. Additionally, objective reflux measurements were only carried out at baseline and not after treatment with drug/placebo. Thus, we had no objective measurement of the effect of lesogaberan on reflux events, or cough–reflux associations. We did not include repeated oesophageal studies in the protocol, as this would have been a very significant burden of invasive monitoring for patients. Finally, we cannot exclude the possibility that lesogaberan might have had a more substantial effect in a subgroup of RCC patients selected for significant reflux–cough associations, *i.e.* a positive SAP.

Conclusion

Lesogaberan demonstrated no effect on objective hourly cough frequency, but reduced the number of cough bouts and capsaicin-evoked cough responses, providing some suggestion of a potential role for peripheral $GABA_B$ receptors in the mechanism of RCC. It is unclear whether the efficacy could be enhanced by selecting patients with greater cough–reflux associations.

Provenance: Submitted article, peer reviewed.

This study is registered at https://eudract.ema.europa.eu/ with identifier number 2014-005074-11 and at https://www.isrctn.com/ with identifier number 77000698. Data are available upon request from the authors.

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B. Al-Sheklly, R.J. Dockry, K. Holt and S. Treadway: recruitment and data collection; H. Badri, J.A. Smith, A. Lee and T. Lee: data analysis. Manuscript written by H. Badri and J.A. Smith, but all authors contributed and reviewed the article.

Conflict of interest: J.A. Smith and K. McGuiness are inventors on a patent describing methods for detecting cough from sound recordings, licensed to Vitalograph Ltd. J.A. Smith has received funding for consultancy and research funds from Afferent Pharmaceuticals, Merck Inc., Bayer, Bellus, GSK, Xention Ltd, Ario Pharma Ltd, Glenmark, Almirall, AstraZeneca, Axalbion, Patara, Verona Pharma, NeRRe Pharmaceuticals, Menlo Pharmaceuticals and Attenua Inc. I. Satia reports grants from the ERS Respire 3 Marie Curie Fellowship, British Medical Association and North West Lung Centre Charity, grants and personal fees from Merck Canada, and personal fees from GSK and AstraZeneca, outside the submitted work. B.J. Canning is on the board of a pharmaceutical company. K.J. Escott is a current employee of AstraZeneca. G. Wilkinson and A. Holt are previous employees of AstraZeneca. H. Badri, C. Gibbard, D. Denton, B. Al-Sheklly, R.J. Dockry, K. Holt, S. Treadway, P. Whorwell, L. Houghton, A. Lee and T. Lee have no conflicts of interests.

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