Clinical trial results:
The Role of GABAb receptor mechanisms in cough: Double-blind randomised controlled trial of Lesogaberan in Chronic cough patients with positive and negative symptom association probabilities

Summary

EudraCT number	2014-005074-11
Trial protocol	GB
Global end of trial date	30 August 2017

Results information

Result version number	v1 (current)
This version publication date	03 June 2020
First version publication date	03 June 2020

Trial information

Trial identification

Sponsor protocol code	14/GAR/002

Additional study identifiers

ISRCTN number	ISRCTN77000698
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	REC reference: 14/NW/1497

Notes:

Sponsors

Sponsor organisation name	Manchester University NHS Foundation Trust
Sponsor organisation address	Oxford Road, Manchester, United Kingdom, M13 9WL
Public contact	Jaclyn Smith, University of Manchester, +44 01612915863, jacky.smith@manchester.ac.uk
Scientific contact	Jaclyn Smith, University of Manchester, +44 01612915863, jacky.smith@manchester.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of 2 weeks of Lesogaberan treatment compared with 2 weeks of placebo treatment on 24 hour cough frequency.

Lay description:

To test what effect a drug called Lesogaberan has on how much a person coughs in a 24 hour period compared to if that person was taking a dummy drug with no active ingredients (called placebo).

Protection of trial subjects:

Patients may experience side effects after taking Lesogaberan or placebo during the study. Lesogaberan has been previously been given to 489 healthy volunteers and 930 patients. The drug was generally well tolerated. The most common side effect of taking Lesogaberan (seen in 1 in 4 people)is tingling or numbness of the fingers, which only mild and temporary. The other side effects were headache (1 in 10), feeling hot, diarrhoea, flatulence and dizziness. During the study patients will be asked to perform a number of tests which may have side effects. Oesophageal studies (high resolution manometry and 24 hour pH impedance). This is a combination of 2
procedures where the patient has a small tube passed through their nose into their stomach, one of the tubes will be left in place for 24 hours. This procedure is not painful, there maybe some slight discomfort when the tube is passed through the nose, thus a numbing agent will be applied to the nasal area to reduce this. there may be some mild gagging or coughing too. Most patients tolerated this procedure well. A cough challenge involves inhaling capsaicin, which is a component of chilli peppers. Capsaicin can cause tightening of the airways, although this is rare. Breathing tests are performed during and after the test to monitor any
chest tightening, which is easily treated by inhaling salbutamol (a medication to open up the airways. Blood tests sometimes cause bruising at the site of the needle puncture. Some people feel faint whilst blood is being withdrawn. Rarely a small blood clot or infection can occur. The electrodes and sticky pads placed on the skin during ECG tests and 24 hour cough monitoring can occasionally lead to skin irritation. Although lung function tests are not painful, they can be tiring to perform. Patients may experience shortness of breath, coughing or chest tightness. Some people can feel lightheaded or faint. A doctor will be present in the department at all times.

Background therapy:

All study participants will continue with their usual clinical treatment and followup via the cough clinic.

Evidence for comparator:

The treatment sequence for each subject number will be randomised. Each subject will receive, in a random order, and in a double-blind fashion, (1) Lesogaberan or (2) Placebo BD in the first dosing period of 14 days. They will then receive the alternate drug/ placebo following a minimum 1 week washout period.

Actual start date of recruitment	23 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	12
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with chronic cough were recruited from the cough specialist clinic at Manchester University NHS Foundation Trust (Wythenshawe Hospital), Manchester, UK. All interested participants were required to read the information sheet carefully and be given at least 24 hours to consider the information before agreeing to take part.

Pre-assignment

Screening details:

27 patients screened; 4 failed screen (uncontrolled hypertension, declined contraceptive measures, current smoker, hypothyroidism), 1 lost to follow up. Inclusion criteria; signed, written, informed consent, age >18yr, compliance with contraceptive measures, BMI 19-35kg/m2 inc, normal spirometry, chronic cough >8weeks, normal CXR.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Randomisation sequences were generated by an external contractor independent to the study site. Blinded study medication and unblinding scratch cards were supplied to the hospital pharmacy department.

Arms

Are arms mutually exclusive?	No
Arm title	Lesogaberan

Arm description:

120mg Lesogaberan MR BD for 2 weeks.

Arm type	Active comparator
Investigational medicinal product name	Lesogaberan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

120mg Lesogaberan (modified release) was taken twice a day at approximately 12 hour intervals. The first dose plus the morning doses on the last two treatment days were taken during study visits whilst in the department to allow measurement of secondary endpoints (blood pK and capsaicin cough response) at peak plasma levels (2 hours post dose).

Arm title	Placebo

Arm description:

2 weeks treatment with matched placebo.

Arm type	Placebo
Investigational medicinal product name	Matched placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matched placebo administered twice a day at approximately 12 hour intervals for 2 weeks. The first dose and morning doses on final two treatment days were taken in the department to allow secondary

endpoint measurements to be taken at peak plasma levels at 2 hours (capsaicin coughs and pK bloods)

Number of subjects in period 1	Lesogaberan	Placebo
Started	22	22
Completed	21	20
Not completed	1	2
Adverse event, non-fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
All patients enrolled in the trial	

Reporting group values	Overall Trial	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	63		
standard deviation	± 7	-	
Gender categorical Units: Subjects			
Female	16	16	
Male	6	6	
Smoking Status Units: Subjects			
Never Smoked	16	16	
Ex Smoker	6	6	
Symptom Association Probability (SAP)			
SAP describes the association between coughing and preceding reflux events. Patients are described being either SAP positive or SAP negative.			
Units: Subjects			
SAP Positive	11	11	
SAP Negative	8	8	
Not recorded	3	3	
Classification of reflux events Units: Subjects			
Normal	17	17	
Abnormal	3	3	
Not recorded	2	2	
Peristalsis Strength Units: Subjects			
Weak	8	8	
Normal	12	12	

Not recorded	2	2	

Smoking History			
Units: Pack Years			
median	0		
inter-quartile range (Q1-Q3)	0 to 2.4	-	
Body Mass Index			
Units: kg/m2			
arithmetic mean	25.8		
standard deviation	± 4.0	-	
Cough Duration			
Units: Years			
median	10.5		
inter-quartile range (Q1-Q3)	5.8 to 17.0	-	
FEV1			
Forced expiratory volume in 1 second			
Units: % predicted			
arithmetic mean	95		
standard deviation	± 14.6	-	
FVC			
Forced vital capacity			
Units: % predicted			
arithmetic mean	110		
standard deviation	± 20.7	-	
24 hour cough frequency			
Baseline cough rate measured over 24 hours during simultaneous impedance pH monitoring			
Units: coughs per hour			
median	24		
inter-quartile range (Q1-Q3)	12 to 32	-	
LCQ Score			
Leicester cough questionnaire total score			
Units: numeric score			
arithmetic mean	14.2		
standard deviation	± 3.8	-	
Daytime cough severity VAS			
100mm visual analogue score			
Units: mm			
arithmetic mean	43		
standard deviation	± 25.6	-	
Night-time cough severity VAS			
100mm visual analogue scale			
Units: mm			
median	17		
inter-quartile range (Q1-Q3)	8 to 25	-	
Symptom Index (SI)			
The symptom index represents the percentage of cough events that correlate with reflux events			
Units: percent			
arithmetic mean			
standard deviation	±	-	
Total reflux episodes			

Units: number median inter-quartile range (Q1-Q3)		- 	
Lower oesophageal sphincter pressure (LOSP)			
Normal pressure - 26mmHg			
Units: mmHg median inter-quartile range (Q1-Q3)		- 	

Subject analysis sets	
Subject analysis set title	SAP Analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description: All patients for whom reflux symptom association data were available (n=19)	
Subject analysis set title	Reflux Analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with fully available reflux data (n=20)	

Reporting group values	SAP Analysis	Reflux Analysis	
Number of subjects	19	20	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years arithmetic mean standard deviation	 ±	 ±	
Gender categorical Units: Subjects			
Female Male			
Smoking Status Units: Subjects			
Never Smoked Ex Smoker			
Symptom Association Probability (SAP)			
SAP describes the association between coughing and preceding reflux events. Patients are described being either SAP positive or SAP negative.			
Units: Subjects			

SAP Positive SAP Negative Not recorded			
Classification of reflux events Units: Subjects			
Normal Abnormal Not recorded			
Peristalsis Strength Units: Subjects			
Weak Normal Not recorded			
Smoking History Units: Pack Years median inter-quartile range (Q1-Q3)			
Body Mass Index Units: kg/m2 arithmetic mean standard deviation	±	±	
Cough Duration Units: Years median inter-quartile range (Q1-Q3)			
FEV1			
Forced expiratory volume in 1 second			
Units: % predicted arithmetic mean standard deviation	±	±	
FVC			
Forced vital capacity			
Units: % predicted arithmetic mean standard deviation	±	±	
24 hour cough frequency			
Baseline cough rate measured over 24 hours during simultaneous impedance pH monitoring			
Units: coughs per hour median inter-quartile range (Q1-Q3)			
LCQ Score			
Leicester cough questionnaire total score			
Units: numeric score arithmetic mean standard deviation	±	±	
Daytime cough severity VAS			
100mm visual analogue score			
Units: mm arithmetic mean standard deviation	±	±	
Night-time cough severity VAS			

100mm visual analogue scale			
Units: mm median inter-quartile range (Q1-Q3)			
Symptom Index (SI)			
The symptom index represents the percentage of cough events that correlate with reflux events			
Units: percent arithmetic mean standard deviation	 14 ± 8.4	 ±	
Total reflux episodes Units: number median inter-quartile range (Q1-Q3)		 48.9 23.5 to 68.8	
Lower oesophageal sphincter pressure (LOSP)			
Normal pressure - 26mmHg			
Units: mmHg median inter-quartile range (Q1-Q3)		 22.2 6.7 to 26.2	

End points

End points reporting groups

Reporting group title	Lesogaberan
Reporting group description:	
120mg Lesogaberan MR BD for 2 weeks.	
Reporting group title	Placebo
Reporting group description:	
2 weeks treatment with matched placebo.	
Subject analysis set title	SAP Analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
All patients for whom reflux symptom association data were available (n=19)	
Subject analysis set title	Reflux Analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with fully available reflux data (n=20)	

Primary: 24-hour Cough Frequency

End point title	24-hour Cough Frequency
End point description:	
End point type	Primary
End point timeframe:	
Cough frequency over 24 hours measured after two weeks treatment with Lesogaberan or matched placebo	

End point values	Lesogaberan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	18		
Units: coughs/hour				
median (inter-quartile range (Q1-Q3))	22.7 (6.7 to 38.8)	22.6 (11.4 to 29.2)		

Statistical analyses

Statistical analysis title	Cough Frequency Analysis
Statistical analysis description:	
Generalised Estimating Equation (GEE) models were used to analyze the data assessing the influence of treatment period and sequence. We adjusted for period specific baseline. Potential carryover effects were examined by the sequence in the model. Based on previous cough frequency data in an unselected chronic cough group, the study had approximately 80% power to detect a 43% reduction in cough with lesogaberan over placebo, assuming a SD of log cough frequency of 0.42. Sig level $p<0.05$.	
Comparison groups	Lesogaberan v Placebo

Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.119 [1]
Method	GEE model

Notes:

[1] - Significance set at p<0.05

Secondary: Capsaicin evoked Emax

End point title	Capsaicin evoked Emax

End point description:

Incremental concentrations of capsaicin were inhaled through a dose controlled nebuliser up to the maximum tolerated dose or the end of the challenge. Emax is defined as the maximum number of coughs evoked by any concentration of capsaicin.

End point type	Secondary

End point timeframe:

Capsaicin challenge was performed at screening and at baseline and at the end of both treatment periods. The challenge was administered at 2 hours post final dose of medication intended to capture peak drug plasma levels.

End point values	Lesogaberan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	16		
Units: Number of coughs				
arithmetic mean (confidence interval 95%)	27.4 (22.7 to 32.1)	34.3 (28.0 to 40.7)		

Statistical analyses

Statistical analysis title	Effect of treatment on maximum cough responses

Statistical analysis description:

Generalised Estimating Equation (GEE) models were used to analyze the data assessing the influence of treatment period and sequence. We adjusted for period specific baseline. Potential carryover effects were examined by the sequence in the model. Significance was set at p <0.05.

Comparison groups	Lesogaberan v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	GEE model

Secondary: Capsaicin evoked ED50

End point title	Capsaicin evoked ED50

End point description:

Capsaicin challenge was performed at screening and at baseline and at the end of both treatment

periods. The challenge was administered at 2 hours post final dose of medication intended to capture peak drug plasma levels.
Incremental concentrations of capsaicin solution were inhaled through a dose controlled nebuliser up to the maximum tolerated dose or the end of the challenge. ED50 is defined as the dose or concentration of capsaicin that elicits half of the maximum cough response (Emax).

End point type	Secondary

End point timeframe:

ED50 dose compared after 2 weeks treatment with lesogaberan or matched placebo.

End point values	Lesogaberan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[2]	16[3]		
Units: micromole(s)				
geometric mean (confidence interval 95%)	45.3 (31.6 to 59.0)	27.7 (15.4 to 39.9)		

Notes:

[2] - 16 out of 22 patients completed the capsaicin challenges due to supply issue.

[3] - 16 out of 22 patients completed the capsaicin challenges due to supply issue.

Statistical analyses

Statistical analysis title	Effect of treatment on capsaicin evoked ED50

Statistical analysis description:

Generalised Estimating Equation (GEE) models were used to analyze the data assessing the influence of treatment period and sequence. We adjusted for period specific baseline. Potential carryover effects were examined by the sequence in the model.

Comparison groups	Lesogaberan v Placebo
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03 [4]
Method	GEE model

Notes:

[4] - Significance set at $p<0.05$

Secondary: Daytime cough severity VAS

End point title	Daytime cough severity VAS

End point description:

100mm visual analogue scale where patients are asked to draw a vertical line to indicate their perceived cough severity during daytime hours on any particular day.

End point type	Secondary

End point timeframe:

Measured pre and post 2 weeks of treatment with lesogaberan or matched placebo.

End point values	Lesogaberan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: millimeter(s)				
median (inter-quartile range (Q1-Q3))	31.5 (22.4 to 61.9)	35.5 (18.3 to 63.5)		

Statistical analyses

Statistical analysis title	Effect of treatment on daytime VAS

Statistical analysis description:

Generalised Estimating Equation (GEE) models were used to analyze the data assessing the influence of treatment period and sequence. We adjusted for period specific baseline. Potential carryover effects were examined by the sequence in the model. Significance was set at $p < 0.05$.

Comparison groups	Lesogaberan v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5
Method	GEE model

Secondary: Night-time cough severity VAS

End point title	Night-time cough severity VAS

End point description:

100mm visual analogue scale where patients are asked to draw a vertical line to indicate their perceived cough severity during overnight hours on any particular day.

End point type	Secondary

End point timeframe:

Measured pre and post 2 weeks of treatment with lesogaberan or matched placebo.

End point values	Lesogaberan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	20		
Units: millimeter(s)				
median (inter-quartile range (Q1-Q3))	12.0 (0.9 to 38.1)	14.5 (2.0 to 36.3)		

Statistical analyses

Statistical analysis title	Effect of treatment on night-time VAS

Statistical analysis description:

Generalised Estimating Equation (GEE) models were used to analyze the data assessing the influence of treatment period and sequence. We adjusted for period specific baseline. Potential carryover effects

were examined by the sequence in the model. Significance was set at p <0.05.

Comparison groups	Lesogaberan v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.768
Method	GEE model

Secondary: LCQ

End point title	LCQ

End point description:

Self-reported quality of life outcome measure - Leicester Cough Questionnaire (LCQ). 19 items with likert scale (1-7) reflecting on cough for previous 2 weeks.

End point type	Secondary

End point timeframe:

Measured pre and post 2 weeks of treatment with lesogaberan or matched placebo

End point values	Lesogaberan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	20		
Units: total score				
arithmetic mean (standard deviation)	14.9 (± 3.0)	14.7 (± 3.5)		

Statistical analyses

Statistical analysis title	Effect of treatment on total LCQ score

Statistical analysis description:

Generalised Estimating Equation (GEE) models were used to analyze the data assessing the influence of treatment period and sequence. We adjusted for period specific baseline. Potential carryover effects were examined by the sequence in the model. Significance was set at p <0.05.

Comparison groups	Lesogaberan v Placebo
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	GEE model

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were reported from administration of the first dose of study medication, throughout both dosing periods (2 weeks each), a 1-2 week washout period and until the final follow up visit (1-2 weeks after final dose of study medication).

Adverse event reporting additional description:

AEs were assessed by the investigator at each study visit via patient reporting, routine safety blood testing, vital signs and ECGs

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo treatment

Reporting group description:

AEs during placebo treatment period

Reporting group title	Lesogaberan treatment

Reporting group description: -

Serious adverse events	Placebo treatment	Lesogaberan treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo treatment	Lesogaberan treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 22 (54.55%)	12 / 21 (57.14%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 22 (18.18%)	1 / 21 (4.76%)	
occurrences (all)	4	1	
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
General disorders and administration			

site conditions Rhinorrhoea subjects affected / exposed occurrences (all)	 0 / 22 (0.00%) 0	 2 / 21 (9.52%) 2	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 2 / 22 (9.09%) 2 0 / 22 (0.00%) 0	 3 / 21 (14.29%) 3 2 / 21 (9.52%) 2 0 / 21 (0.00%) 0 2 / 21 (9.52%) 2	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all)	 2 / 22 (9.09%) 2 2 / 22 (9.09%) 2	 3 / 21 (14.29%) 3 0 / 21 (0.00%) 0	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 1 / 22 (4.55%) 1	 2 / 21 (9.52%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 February 2017	Substantial Amendment number 1: Section 9.1, page 29, of the protocol was updated to reduce the total number of patients recruited to the study from 50 to 25. As recruitment commenced the investigators noticed a self-selection bias in the study, with only the patients who have reflux agreeing to take part. Thus the vast majority of the patients recruited and tested being SAP positive. If SAP positive vs SAP negative patients were compared as part of the secondary outcome of the study, a very large number of patients would have been needed. Whereas if only SAP positive patients were studied, only need 25 patients would be required (based on previous studies calculations).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported