



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 is 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 may be 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 inter-quartile range (Q1-Q3) | 0 0 to 2.4 | - | |
| Body Mass Index Units: kg/m2 arithmetic mean standard deviation | 25.8 ± 4.0 | - | |
| Cough Duration Units: Years median inter-quartile range (Q1-Q3) | 10.5 5.8 to 17.0 | - | |
| FEV1 | | | |
| Forced expiratory volume in 1 second | | | |
| Units: % predicted arithmetic mean standard deviation | 95 ± 14.6 | - | |
| FVC | | | |
| Forced vital capacity | | | |
| Units: % predicted arithmetic mean standard deviation | 110 ± 20.7 | - | |
| 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) | 24 12 to 32 | - | |
| LCQ Score | | | |
| Leicester cough questionnaire total score | | | |
| Units: numeric score arithmetic mean standard deviation | 14.2 ± 3.8 | - | |
| Daytime cough severity VAS | | | |
| 100mm visual analogue score | | | |
| Units: mm arithmetic mean standard deviation | 43 ± 25.6 | - | |
| Night-time cough severity VAS | | | |
| 100mm visual analogue scale | | | |
| Units: mm median inter-quartile range (Q1-Q3) | 17 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 (\pm 3.0) | 14.7 (\pm 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 | 0 / 22 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 3 / 21 (14.29%) | |
| occurrences (all) | 1 | 3 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 21 (9.52%) | |
| occurrences (all) | 1 | 2 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 3 / 21 (14.29%) | |
| occurrences (all) | 2 | 3 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 21 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 21 (9.52%) | |
| occurrences (all) | 1 | 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