Clinical trial results:
A randomised, placebo controlled trial of extra-oesophageal reflux treatment in the management of upper respiratory symptoms. [TOPPITS: Trial of Proton Pump Inhibitors in Throat Symptoms]

Summary

EudraCT number	2013-004249-17
Trial protocol	GB
Global end of trial date	23 March 2018

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	NCTU:6831

Additional study identifiers

ISRCTN number	ISRCTN38578686
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Newcastle upon Tyne Hospitals NHS Foundation Trust
Sponsor organisation address	Joint Research Office, Level 1, Regent Point, Regent Farm Road, Gosforth, Newcastle upon Tyne, United Kingdom,
Public contact	Janet Wilson, Newcastle University, 0191 2231086, janet.wilson@ncl.ac.uk
Scientific contact	Janet Wilson, Newcastle University, 0191 2231086, janet.wilson@ncl.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	23 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 March 2018
Global end of trial reached?	Yes
Global end of trial date	23 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the symptomatic response in patients with persistent throat symptoms at the end of four months' (16 weeks') therapy of treatment with lansoprazole versus placebo.

Protection of trial subjects:

None

Background therapy:

None

Evidence for comparator:

Placebo control was chosen for this trial, as Extra Oesophageal Reflux (EOR) symptoms have long been recognised as having a strong placebo response. There is a growing trend to treat throat symptom patients empirically with proton pump inhibitors (PPIs), but most controlled studies fail to demonstrate a significant benefit of PPI over placebo. Hence, a placebo-controlled trial was chosen, to establish any benefit.

Actual start date of recruitment	03 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 346
Worldwide total number of subjects	346
EEA total number of subjects	346

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)	267

From 65 to 84 years	79
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment period ran from 27 May 2014 until 28 February 2017, at eight NHS hospital sites in the United Kingdom. Sites were in Newcastle upon Tyne, Sunderland, Nottingham, Brighton, Manchester, Birmingham and Stockport in England, and Glasgow in Scotland.

Pre-assignment

Screening details:

Potential participants will be referred direct from primary care, or by scrutiny of hospital/GP/primary care referral letters. All eligible (RSI ≥10), potential participants will be informed about TOPPITS, receive an invitation letter and PIS in the post, and be booked onto a TOPPITS screening clinic.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Placebo-matched capsules were made, to establish the blind from trial start. Sealed codebreak envelopes were stored in the Pharmacy/ISF, and opened only in an emergency, with CI authorisation. If the code was broken, participant number, staff name, why and when were recorded. At 12 months, participants were asked if they thought they were on lansoprazole or placebo, and why. The blind was maintained until all trial data were collected and the database locked, when participants were unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

Lansoprazole 30 mg bd

Arm type	Experimental
Investigational medicinal product name	Lansoprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30 mg bd

Arm title	Placebo

Arm description:

Matching placebo twice-daily

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

Dosage and administration details:

One tablet, bd

Number of subjects in period 1	Treatment	Placebo
Started	172	174
Completed	172	174

Period 2

Period 2 title	16 weeks' participation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Placebo-matched capsules were made, to establish the blind from trial start. Sealed code-break envelopes were stored in the Pharmacy/ISF, and opened only in an emergency, with CI authorisation. If the code was broken, participant number, staff name, why and when were recorded. At 12 months, participants were asked if they thought they were on lansoprazole or placebo, and why. The blind was maintained until all trial data were collected and the database locked, when participants were unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

Lansoprazole 30 mg bd

Arm type	Experimental
Investigational medicinal product name	Lansoprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

30mg bd

Arm title	Placebo

Arm description:

Matched placebo bd

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

Dosage and administration details:

One tablet, bd

Number of subjects in period 2	Treatment	Placebo
Started	172	174
Completed	135	148
Not completed	37	26
Lost to follow-up	37	26

Period 3

Period 3 title	12 months' participation
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Assessor

Blinding implementation details:

Placebo-matched capsules were made, to establish the blind from trial start. Sealed code-break envelopes were stored in the Pharmacy/ISF, and opened only in an emergency, with CI authorisation. If the code was broken, participant number, staff name, why and when were recorded. At 12 months, participants were asked if they thought they were on lansoprazole or placebo, and why. The blind was maintained until all trial data were collected and the database locked, when participants were unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

Lansoprazole 30 mg bd

Arm type	Experimental
Investigational medicinal product name	Lansoprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

30 mg bd

Arm title	Placebo

Arm description:

Matched placebo 30 mg bd

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

Dosage and administration details:

One tablet, bd

Number of subjects in period 3	Treatment	Placebo
Started	135	148
Completed	109	117
Not completed	26	31
Lost to follow-up	26	31

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description: Lansoprazole 30 mg bd	
Reporting group title	Placebo
Reporting group description: Matching placebo twice-daily	

Reporting group values	Treatment	Placebo	Total
Number of subjects	172	174	346
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			
The subject population was adults of age 18 and over.			
Units: years			
arithmetic mean	53.5	50.8	
full range (min-max)	21 to 84	20 to 80	-
Gender categorical			
Subjects were both male and female.			
Units: Subjects			
Female	101	95	196
Male	71	79	150
Site			
Trial site at which the participant was recruited.			
Units: Subjects			
Birmingham	5	5	10
Brighton	5	4	9
Glasgow	18	21	39
Manchester	15	12	27
Newcastle	66	67	133
Nottingham	34	36	70
Stockport	5	6	11
Sunderland	24	23	47
Weight			
Weight of participant.			
Units: kg			

arithmetic mean	79.4	79.3	
standard deviation	± 18.2	± 16.8	-
Height			
Height of participant.			
Units: metres			
arithmetic mean	1.68	1.68	
standard deviation	± 0.12	± 0.10	-
Body Mass Index (BMI)			
Body Mass Index of participants.			
Units: BMI			
arithmetic mean	28.2	28.1	
standard deviation	± 5.9	± 5.3	-
Smoking pack years			
Smoking habits of participants.			
Units: number			
median	0	0	
inter-quartile range (Q1-Q3)	0 to 0	0 to 5	-
Alcohol consumption			
Alcohol consumption of participants.			
Units: Units per week			
median	4	3	
inter-quartile range (Q1-Q3)	0 to 10	0 to 10	-
Baseline severity (RSI-HB)			
Baseline severity of throat symptoms (RSI score less heartburn score) for participants.			
Units: RSI units			
arithmetic mean	20.0	20.1	
standard deviation	± 6.8	± 6.5	-

Subject analysis sets

Subject analysis set title	All trial participants
Subject analysis set type	Full analysis

Subject analysis set description:

This covers all trial participants, whether compliant or not.

Subject analysis set title	Pragmatic ITT group
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A distribution approach was used to determine a clinically relevant compliance window, to maximise inclusion of participants and exclude only significant outliers. Thus the compliant ITT group was defined, including all ineligible and protocol violator participants, in their randomised treatment groups, attending the 16-week follow-up visit at any time, and completing outcome measures at any time point. Secondary analysis, of the primary outcome measure, was of this group.

Subject analysis set title	Compliant Intention to Treat (ITT) group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A distribution approach was used to determine a clinically relevant compliance window, to maximise inclusion of participants and exclude only significant outliers. Thus the compliant ITT group was defined, including all ineligible and protocol violator participants, in their randomised treatment groups, attending the 16-week follow-up visit between 14 and 20 weeks, and completing outcome measures within 14 to 20 weeks of randomisation. Primary comparative analyses were of this group.

Reporting group values	All trial participants	Pragmatic ITT group	Compliant Intention to Treat (ITT) group
Number of subjects	346	267	220
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			
The subject population was adults of age 18 and over.			
Units: years			
arithmetic mean	52.2	53.5	54.5
full range (min-max)	20 to 84	21 to 84	21 to 84
Gender categorical			
Subjects were both male and female.			
Units: Subjects			
Female	196	153	126
Male	150	114	94
Site			
Trial site at which the participant was recruited.			
Units: Subjects			
Birmingham	10	9	9
Brighton	9	7	5
Glasgow	39	25	19
Manchester	27	23	15
Newcastle	133	97	69
Nottingham	70	64	63
Stockport	11	11	9
Sunderland	47	31	31
Weight			
Weight of participant.			
Units: kg			
arithmetic mean	79.4	78.7	79.5
standard deviation	± 17.5	± 17.3	± 17.8
Height			
Height of participant.			
Units: metres			
arithmetic mean	1.68	1.67	1.67
standard deviation	± 0.11	± 0.10	± 0.12
Body Mass Index (BMI)			
Body Mass Index of participants.			
Units: BMI			
arithmetic mean	28.1	28.1	28.5
standard deviation	± 5.6	± 5.8	± 6.1
Smoking pack years			

Smoking habits of participants.			
Units: number			
median	0	0	0
inter-quartile range (Q1-Q3)	0 to 3	0 to 2.5	0 to 1
Alcohol consumption			
Alcohol consumption of participants.			
Units: Units per week			
median	4	3	4
inter-quartile range (Q1-Q3)	0 to 10	0 to 10	0 to 10
Baseline severity (RSI-HB)			
Baseline severity of throat symptoms (RSI score less heartburn score) for participants.			
Units: RSI units			
arithmetic mean	20.1	20.0	20.0
standard deviation	± 6.6	± 6.7	± 7.0

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description: Lansoprazole 30 mg bd	
Reporting group title	Placebo
Reporting group description: Matching placebo twice-daily	
Reporting group title	Treatment
Reporting group description: Lansoprazole 30 mg bd	
Reporting group title	Placebo
Reporting group description: Matched placebo bd	
Reporting group title	Treatment
Reporting group description: Lansoprazole 30 mg bd	
Reporting group title	Placebo
Reporting group description: Matched placebo 30 mg bd	
Subject analysis set title	All trial participants
Subject analysis set type	Full analysis
Subject analysis set description: This covers all trial participants, whether compliant or not.	
Subject analysis set title	Pragmatic ITT group
Subject analysis set type	Intention-to-treat
Subject analysis set description: A distribution approach was used to determine a clinically relevant compliance window, to maximise inclusion of participants and exclude only significant outliers. Thus the compliant ITT group was defined, including all ineligible and protocol violator participants, in their randomised treatment groups, attending the 16-week follow-up visit at any time, and completing outcome measures at any time point. Secondary analysis, of the primary outcome measure, was of this group.	
Subject analysis set title	Compliant Intention to Treat (ITT) group
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: A distribution approach was used to determine a clinically relevant compliance window, to maximise inclusion of participants and exclude only significant outliers. Thus the compliant ITT group was defined, including all ineligible and protocol violator participants, in their randomised treatment groups, attending the 16-week follow-up visit between 14 and 20 weeks, and completing outcome measures within 14 to 20 weeks of randomisation. Primary comparative analyses were of this group.	

Primary: RSI score at 16 weeks

End point title	RSI score at 16 weeks
End point description: Symptomatic response measured using the Reflux Symptom Index (RSI) in patients with persistent throat symptoms at the end of 16 weeks' therapy with lansoprazole versus placebo. The RSI score is calculated from a nine-item, self-administered questionnaire scored on a Likert scale with each item score ranging from 0-5 giving a total score range of 0-45. A higher score indicates more severe symptoms.	
End point type	Primary
End point timeframe: 16 weeks post-randomisation.	

End point values	Treatment	Placebo	Pragmatic ITT group	Pragmatic ITT group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	127	140	127	140
Units: no units				
arithmetic mean (confidence interval 95%)	17.1 (15.5 to 18.8)	16.0 (14.4 to 17.6)	17.1 (15.5 to 18.8)	16.0 (14.4 to 17.6)

End point values	Compliant Intention to Treat (ITT) group	Compliant Intention to Treat (ITT) group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	102	118		
Units: no units				
arithmetic mean (confidence interval 95%)	17.4 (15.5 to 19.4)	15.6 (13.8 to 17.3)		

Statistical analyses

Statistical analysis title	Two sample t test compliant ITT group

Statistical analysis description:

Univariate analysis of unadjusted primary outcome measure for compliant analysis group.

Comparison groups	Compliant Intention to Treat (ITT) group v Compliant Intention to Treat (ITT) group
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	= 0.162 [2]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	4.487
Variability estimate	Standard error of the mean
Dispersion value	1.33

Notes:

[1] - The primary hypothesis to be tested is H0: The mean RSI scores at primary end-point (16-week visit) are equal for both arms (lansoprazole v placebo). A two-sided significance level of $p<0.05$ is used throughout.

[2] - Test statistic: t=1.402, two-sided P-value= 0.162, concluding that there is no statistically significant difference in the RSI score at 16 weeks between lansoprazole and placebo.

Statistical analysis title	Multilevel mixed effect linear regression

Statistical analysis description:

Adjusted for stratification factor recruiting centre (as a random effect) at randomisation and baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect).

Comparison groups	Compliant Intention to Treat (ITT) group v Compliant Intention to Treat (ITT) group
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	= 0.196 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	3.5
Variability estimate	Standard error of the mean
Dispersion value	1.091

Notes:

[3] - The continuous covariate (RSI-HB) was explored to assess whether transformation of RSI-HB was a better fit to the relationship with outcome than an untransformed continuous measure based on a reduction in Akaike information criterion (AIC). There was no reduction in AIC so to build the most parsimonious, clinically interpretable model, RSI-HB was retained as an un-transformed continuous covariate, under the assumption of linearity with outcome

[4] - There is no statistically significant difference between randomised arms, lansoprazole compared to placebo (p=0.196), when adjusted for site and baseline continuous RSI-HB.

Statistical analysis title	Two sample t test pragmatic ITT group

Statistical analysis description:

Univariate analysis of unadjusted primary outcome measure for compliant analysis group.

Comparison groups	Pragmatic ITT group v Pragmatic ITT group
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.309 [6]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.11
upper limit	3.5
Variability estimate	Standard error of the mean
Dispersion value	1.17

Notes:

[5] - The secondary hypothesis to be tested is H0: The mean RSI scores at primary end-point (16-week visit) are equal for both arms (lansoprazole v placebo). A two-sided significance level of $p<0.05$ is used throughout.

[6] - Test statistic: t=1.020, two-sided P-value= 0.154, concluding that there is no statistically significant difference in the RSI score at 16 weeks between lansoprazole and placebo.

Statistical analysis title	Multilevel mixed effect linear regression

Statistical analysis description:

Adjusted for stratification factor recruiting centre (as a random effect) at randomisation and baseline severity in terms of RSI-HB as a continuous measure (as a fixed effect).

Comparison groups	Pragmatic ITT group v Pragmatic ITT group
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	equivalence[7]
P-value	= 0.264 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	3.05
Variability estimate	Standard error of the mean
Dispersion value	0.99

Notes:

[7] - The continuous covariate (RSI-HB) was explored to assess whether transformation of RSI-HB was a better fit to the relationship with outcome than an untransformed continuous measure based on a reduction in Akaike information criterion (AIC). There was no reduction in AIC so to build the most parsimonious, clinically interpretable model, RSI-HB was retained as an un-transformed continuous covariate, under the assumption of linearity with outcome

[8] - There is no statistically significant difference between randomised arms, lansoprazole compared to placebo (p=0.264), when adjusted for site and baseline continuous RSI-HB.

Secondary: RSI at 12 months

End point title	RSI at 12 months

End point description:

End point type	Secondary

End point timeframe:

This is RSI score at 12 months' participation - eight months after the end of the treatment period.

End point values	Treatment	Placebo	Compliant Intention to Treat (ITT) group	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	99	181	
Units: none				
arithmetic mean (confidence interval 95%)	16.0 (13.6 to 18.4)	13.6 (11.7 to 15.5)	14.7 (13.2 to 16.2)	

Statistical analyses

Statistical analysis title	Univariate analysis of unadjusted 2-sample t-test

Statistical analysis description:

Univariate analysis of unadjusted primary outcome measure for compliant analysis group at 12 months.

Comparison groups	Treatment v Placebo v Compliant Intention to Treat (ITT) group
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.115 [9]
Method	t-test, 2-sided
Parameter estimate	Mean difference (net)
Point estimate	2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	5.414
Variability estimate	Standard error of the mean
Dispersion value	1.52

Notes:

[9] - Test statistic: t=1.583, two-sided P-value= 0.115, concluding that there is no statistically significant difference in the RSI score at 12 months between lansoprazole and placebo.

Statistical analysis title	Multivariable analysis of RSI at 12 months

Statistical analysis description:

Compliant ITT group

Comparison groups	Treatment v Placebo v Compliant Intention to Treat (ITT) group
Number of subjects included in analysis	362
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.157 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	4.1
Variability estimate	Standard error of the mean
Dispersion value	1.22

Notes:

[10] - No statistically significant difference between lansoprazole and placebo, when adjusted for site and baseline continuous RSI-HB. Estimated difference that lansoprazole participants have RSI score at 12 months 1.7 points higher (worse) than placebo.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All non-SAEs/SARs occurring during drug treatment were reported on the eCRF system within four weeks of the form being due.

Adverse event reporting additional description:

All Adverse Events were recorded. PIs were responsible for managing all AEs/ARs according to local protocols.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Treatment

Reporting group description:

Participants receiving active treatment.

Reporting group title	Placebo

Reporting group description:

Participants receiving placebo.

Serious adverse events	Treatment	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 172 (1.16%)	2 / 174 (1.15%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Papillary thyroid carcinoma	Additional description: Left hemithyroidectomy for BA lesion, the cause of which was found to be papillary thyroid carcinoma.		
subjects affected / exposed	2 / 172 (1.16%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Asthma	Additional description: Exacerbation of asthma.		
subjects affected / exposed	2 / 172 (1.16%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Unintentional digestion of bleach/cleaning fluid			

subjects affected / exposed	2 / 172 (1.16%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Collapse	Additional description: Transient loss of consciousness, followed by collapse.		
subjects affected / exposed	2 / 172 (1.16%)	2 / 174 (1.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Treatment	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Surgical and medical procedures			
Colonoscopy			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Elective surgery			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Insertion of septal button			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Headaches, stomach pains			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	

Sickness			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Voice fatigue			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Immune system disorders			
Allergy			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Respiratory, thoracic and mediastinal disorders			
Cold			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Cough			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Sore throat			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Upper respiratory tract infection			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Nasal polyps			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Nasal sores			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Pulmonary oedema			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Psychiatric disorders			
Low mood			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	

Depression			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Injury, poisoning and procedural complications			
Electric shock			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Cardiac disorders			
Cardiac symptoms			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Nervous system disorders			
Headache			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Migraine			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Amnesia			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Numbness			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Pins and needles			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Eye disorders			
Peripheral vision disturbance			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Swollen eyes			

subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Eye ulcer			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Constipation			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Diarrhoea			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Flatulence			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Food poisoning			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Gastrointestinal symptoms			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Indigestion			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Nausea			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Pain, upper right quadrant			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Stomach ache			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	

Vomiting			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Colic			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Dry mouth			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Dyspepsia			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Mouth ulceration			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Swallowing difficult			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Hepatobiliary disorders			
Gallbladder disorder			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Back pain			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Polyarthritis			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	

Pain in joints			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Infections and infestations			
Chest infection			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Flu			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Viral throat infection			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Ear infection			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Gum infection			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Helicobacter infection			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Tonsillitis			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	
Viral infection			
subjects affected / exposed	39 / 172 (22.67%)	35 / 174 (20.11%)	
occurrences (all)	60	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2015	IMP Label: • Wording changed for emergency contact details Protocol changes: • Eligibility criteria clarified • Addition of information on washout periods prior to study participation • Addition of 'You are in a washout period' card to provide to participants • Provision for participants to find out whether their treatment, post-trial • Administrative changes to protocol Addition of new site: University Hospitals Birmingham NHS Foundation Trust Addition of PIC into Manchester: Tameside Hospital NHS Foundation Trust Change of PI at the Sunderland site Additions to PIS and ICF for Birmingham site Study poster and GP/Clinician Summary Information Sheet
07 December 2015	New Statistician working on trial Protocol updates: • Clarified wording of consent-washout-randomisation process • Revised 'Schedule of Events' table • Amended details of use of DVD • Clarified blinding arrangements • Clarified timescales for laryngoscopy Added new site: Stockport NHS Foundation Trust Added PIC site into Stockport: University Hospital of South Manchester NHS Foundation Trust (now re-named Manchester University NHS Foundation Trust) Clarified use of 'internal PICs' in Scotland
07 December 2015	Change of PI at Sunderland site
07 December 2015	Updated Reference Safety Information (RSI) for the trial, in response to risk assessment. Correction of exclusion criteria, in response to minor safety issue. Correction of Statistician name updated as part of previous Amendment, but not included in protocol at that time.
03 March 2017	Change in Principal Investigator at the Sunderland site Addition of Senior Clinical Trial Statistician to the trial team, who replaces current Statistician as signatory on trial protocol Minor updates to trial protocol Update of relevant authorities of Funder-approved extension of trial, including exceeding planned sample size

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Despite extensive efforts, the PPI strand of the trial proved disappointing. Improvements could be made to investigate reasons for non-engagement, consulting patients who declined participation or with other symptoms, and involving site staff more.

Notes: