



Clinical trial results:

A 2x2 factorial randomised examiner blind open label trial to determine the CLinical and cost- Effectiveness of hypertonic saline (HTS 6%) and carbocisteine for Airway cleaRance versus usual care over 52 weeks in bronchiectasis

Summary

EudraCT number	2017-000664-14
Trial protocol	GB
Global end of trial date	24 September 2024

Results information

Result version number	v1 (current)
This version publication date	01 January 2026
First version publication date	01 January 2026

Trial information

Trial identification

Sponsor protocol code	16178SE-AS
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Additional study identifiers

ISRCTN number	ISRCTN89040295
ClinicalTrials.gov id (NCT number)	NCT04140214
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health and Social Care Trust
Sponsor organisation address	Non Clinical Support Building, Royal Victoria Hospital, 274 Grosvenor Road, Belfast, Belfast, United Kingdom, BT9 7AB
Public contact	Professor Judy Bradley, Queens University Belfast, 00 44 2895047973, judy.bradley@qub.ac.uk
Scientific contact	Professor Judy Bradley, Queens University Belfast, 00 44 2895047973, judy.bradley@qub.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	18 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 September 2024
Global end of trial reached?	Yes
Global end of trial date	24 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aims to find out if hypertonic saline (salty water) or carbocisteine or a combination of both is most effective at reducing the number of exacerbations in people with bronchiectasis following 52 weeks of treatment.

People with bronchiectasis have chronic sputum production and both hypertonic saline and carbocisteine can help people with bronchiectasis clear their chest. Research has shown that these agents can make it easier for patients to cough up sputum resulting in potentially fewer exacerbations requiring antibiotics and hospital admissions.

Protection of trial subjects:

A small number of this patient population experience small side effects from nebulising hypertonic saline (HTS) e.g. wheeze.

The likelihood of this will be minimised by all patients assigned hypertonic saline completing a drug response assessment on entry into the study.

A small number of patients experience some minimal side effects (stomach discomfort, vomiting, skin rashes and allergies) associated with carbocisteine.

The PI or designee recorded all directly observed Adverse Events and all Adverse Events spontaneously reported by the patient. Any complications were treated as per the standard procedure for the treating clinician.

A Data Monitoring and Ethics Committee (DMEC) was also convened will containing experts in respiratory medicine.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	01 January 2018
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: 288
Worldwide total number of subjects	288
EEA total number of subjects	0

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)	103
From 65 to 84 years	181
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

288 patients were recruited between 27/06/2018 and 28/09/2023 from UK based centres.

Pre-assignment

Screening details:

Overall 2804 patients were assessed for eligibility for the CLEAR Trial.

Of these 288 were recruited to the study.

Of those 288 patients recruited, 46 patients completed a 30-day washout of mucoactive treatment prior to recruitment.

Pre-assignment period milestones

Number of subjects started	288
Number of subjects completed	288

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention 1: HTS (6%)

Arm description:

Standard care and twice daily nebulised HTS (6%) over 52 weeks

Arm type	Experimental
Investigational medicinal product name	Mucoclear Hypertonic Saline (6%)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Administer a 1 x 4 mL ampoule twice daily for 52 weeks using the e-Flow nebuliser.

Arm title	Intervention 2: Carbocisteine
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Arm description:

Standard care and carbocisteine (750 mg three times per day until visit 3 reducing to 750 mg two times per day) over 52 weeks.

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

Dosage and administration details:

2 x 375 mg oral capsules three times daily until visit 3. At visit 3 patients were instructed to reduce their dose to 2 x 375 mg capsules twice daily for the remainder of the 52 weeks.

Arm title	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
Arm description: Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg of three times per day until visit 3 reducing to 750 mg twice per day) over 52 weeks.	
Arm type	Active comparator
Investigational medicinal product name	Mucoclear Hypertonic Saline (6%)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use
Dosage and administration details: Administer a 1 x 4 mL ampoule twice daily for 52 weeks using the e-Flow nebuliser.	
Investigational medicinal product name	Carbocisteine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 2 x 375 mg oral capsules three times daily until visit 3. At visit 3 patients were instructed to reduce their dose to 2 x 375 mg capsules twice daily for the remainder of the 52 weeks.	
Arm title	Control: Standard Care
Arm description: Standard care over 52 weeks	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Intervention 1: HTS (6%)	Intervention 2: Carbocisteine	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
Started	73	71	73
Completed	67	70	59
Not completed	6	1	14
did not reach week 8 as per mITT definition	6	1	14

Number of subjects in period 1	Control: Standard Care
Started	71
Completed	71
Not completed	0
did not reach week 8 as per mITT definition	-

Baseline characteristics

Reporting groups

Reporting group title	Intervention 1: HTS (6%)
Reporting group description:	
Standard care and twice daily nebulised HTS (6%) over 52 weeks	
Reporting group title	Intervention 2: Carbocisteine
Reporting group description:	
Standard care and carbocisteine (750 mg three times per day until visit 3 reducing to 750 mg two times per day) over 52 weeks.	
Reporting group title	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
Reporting group description:	
Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg of three times per day until visit 3 reducing to 750 mg twice per day) over 52 weeks.	
Reporting group title	Control: Standard Care
Reporting group description:	
Standard care over 52 weeks	

Reporting group values	Intervention 1: HTS (6%)	Intervention 2: Carbocisteine	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
Number of subjects	73	71	73
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	63.5	66.0	67.2
standard deviation	± 14.0	± 13.2	± 13.0
Gender categorical Units: Subjects			
Female	38	47	48
Male	35	24	25
Ethnicity Units: Subjects			
White	72	67	70
Asian/Asian British	1	1	1
Indian	0	1	0
Chinese	0	1	0
Black/African/Caribbean/Black British	0	1	1

African	0	0	1
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Height Units: metre arithmetic mean standard deviation	168.5 ± 7.9	164.6 ± 9.9	163.6 ± 9.5
Weight Units: kilogram(s) arithmetic mean standard deviation	79.6 ± 16.4	71.1 ± 16.9	75.2 ± 17.8
Temperature Units: celsius temperature arithmetic mean standard deviation	36.4 ± 0.6	36.5 ± 0.4	36.5 ± 0.4
Systolic BP Units: mmHg arithmetic mean standard deviation	136.4 ± 18.3	135.7 ± 18.1	135.1 ± 14.0
Diastolic BP Units: mmHg arithmetic mean standard deviation	77.8 ± 10.0	76.0 ± 9.1	77.3 ± 8.4
Pulse Units: BPM arithmetic mean standard deviation	72.1 ± 14.0	71.7 ± 10.3	72.7 ± 10.7
Respiratory Rate Units: per minute arithmetic mean standard deviation	16.7 ± 2.8	16.9 ± 2.3	16.8 ± 2.5
SpO2 Units: Percentage arithmetic mean standard deviation	96.5 ± 1.3	96.2 ± 1.9	96.2 ± 1.7
BSI Score Units: Number arithmetic mean standard deviation	6.8 ± 3.3	7.9 ± 2.8	7.1 ± 3.3
FACED Score Units: Number arithmetic mean standard deviation	1.9 ± 1.6	2.4 ± 1.4	2.0 ± 1.4

Reporting group values	Control: Standard Care	Total	
Number of subjects	71	288	
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	66.3		
standard deviation	± 11.5	-	
Gender categorical			
Units: Subjects			
Female	38	171	
Male	33	117	
Ethnicity			
Units: Subjects			
White	69	278	
Asian/Asian British	0	3	
Indian	1	2	
Chinese	1	2	
Black/African/Caribbean/Black British	0	2	
African	0	1	
Height			
Units: metre			
arithmetic mean	166.7		
standard deviation	± 9.8	-	
Weight			
Units: kilogram(s)			
arithmetic mean	80.3		
standard deviation	± 16.6	-	
Temperature			
Units: celsius temperature			
arithmetic mean	36.4		
standard deviation	± 0.5	-	
Systolic BP			
Units: mmHg			
arithmetic mean	136.3		
standard deviation	± 18.6	-	
Diastolic BP			
Units: mmHg			
arithmetic mean	77.9		
standard deviation	± 9.0	-	
Pulse			
Units: BPM			
arithmetic mean	72.9		
standard deviation	± 10.9	-	
Respiratory Rate			
Units: per minute			
arithmetic mean	16.8		

standard deviation	± 2.1	-	
SpO2			
Units: Percentage			
arithmetic mean	96.4		
standard deviation	± 1.4	-	
BSI Score			
Units: Number			
arithmetic mean	7.7		
standard deviation	± 3.5	-	
FACED Score			
Units: Number			
arithmetic mean	2.2		
standard deviation	± 1.4	-	

End points

End points reporting groups

Reporting group title	Intervention 1: HTS (6%)
Reporting group description: Standard care and twice daily nebulised HTS (6%) over 52 weeks	
Reporting group title	Intervention 2: Carbocisteine
Reporting group description: Standard care and carbocisteine (750 mg three times per day until visit 3 reducing to 750 mg two times per day) over 52 weeks.	
Reporting group title	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
Reporting group description: Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg of three times per day until visit 3 reducing to 750 mg twice per day) over 52 weeks.	
Reporting group title	Control: Standard Care
Reporting group description: Standard care over 52 weeks	

Primary: Mean number of exacerbations over 52 weeks

End point title	Mean number of exacerbations over 52 weeks
End point description: Mean number of exacerbations over 52 weeks	
End point type	Primary
End point timeframe: Randomisation (Baseline) until week 52	

End point values	Intervention 1: HTS (6%)	Intervention 2: Carbocisteine	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine	Control: Standard Care
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	70	59	71
Units: Number				
arithmetic mean (standard deviation)	0.75 (\pm 1.08)	0.93 (\pm 0.94)	0.78 (\pm 1.18)	1.04 (\pm 1.54)

Statistical analyses

Statistical analysis title	Primary Outcome: HTS vs No
Statistical analysis description: HTS vs No i.e. Group 1&3 vs Group 2&4 Mean number of exacerbations over 52 weeks	
Comparison groups	Intervention 1: HTS (6%) v Intervention 2: Carbocisteine v Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine v Control: Standard Care

Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.119
Method	Negative Binomial Regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	0.07

Notes:

[1] - Unadjusted

Statistical analysis title	Primary Outcome: CARB vs No
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Statistical analysis description:

CARB vs No i.e. Group 2&3 vs Group 1&4

Mean number of exacerbations over 52 weeks

Comparison groups	Intervention 1: HTS (6%) v Intervention 2: Carbocisteine v Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine v Control: Standard Care
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.792
Method	Negative Binomial Regression
Parameter estimate	Mean difference (final values)
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.28

Notes:

[2] - Unadjusted

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for the trial begins upon enrolment into the trial and ends 30 days following the last administration of the study drug.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	4

Reporting groups

Reporting group title	Intervention 1: HTS (6%)
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Reporting group description:

Standard care and twice daily nebulised HTS (6%) over 52 weeks

Reporting group title	Intervention 2: Carbocisteine
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Reporting group description:

Standard care and carbocisteine (750 mg three times per day until visit 3 reducing to 750 mg two times per day) over 52 weeks.

Reporting group title	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
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Reporting group description:

Standard care and combination of twice daily nebulised HTS (6%) and carbocisteine (750 mg of three times per day until visit 3 reducing to 750 mg twice per day) over 52 weeks.

Reporting group title	Control: Standard Care
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Reporting group description:

Standard care over 52 weeks

Serious adverse events	Intervention 1: HTS (6%)	Intervention 2: Carbocisteine	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 72 (8.33%)	10 / 72 (13.89%)	10 / 69 (14.49%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Fall			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myasthenia gravis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular Tachycardia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Cholecystectomy			

subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip surgery			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Vertigo postional			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Appendicitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bleeding Duodenal Ulcer			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colecystitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis Ischaemic			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal Obstruction			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Atrial Fibrillation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Sebacious Cyst			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Control: Standard Care		
Total subjects affected by serious			

adverse events			
subjects affected / exposed	9 / 71 (12.68%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pelvic fracture			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Fall			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myasthenia gravis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial Infarction			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Palpitations			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular Tachycardia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip surgery			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Vertigo postional			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Appendicitis			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bleeding Duodenal Ulcer			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colecystitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis Ischaemic			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intestinal Obstruction			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Atrial Fibrillation			

subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Sebacious Cyst			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Pyelonephritis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Joint effusion			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Influenza			

subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Intervention 1: HTS (6%)	Intervention 2: Carbocisteine	Intervention 3: Mucoclear Hypertonic Saline and Carbocisteine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 72 (69.44%)	53 / 72 (73.61%)	50 / 69 (72.46%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Large intestine polyp			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Lipoma			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Prostate cancer			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Headache			
subjects affected / exposed	3 / 72 (4.17%)	3 / 72 (4.17%)	2 / 69 (2.90%)
occurrences (all)	3	3	2
Vascular disorders			
Aortic aneurysm			

subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Circulatory collapse			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	2	0
Dizziness			
subjects affected / exposed	3 / 72 (4.17%)	3 / 72 (4.17%)	2 / 69 (2.90%)
occurrences (all)	3	3	2
Dyspnoea			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Peripheral swelling			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Pulmonary embolism			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Syncope			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Varicose vein			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Cataract Operation			
subjects affected / exposed	0 / 72 (0.00%)	3 / 72 (4.17%)	1 / 69 (1.45%)
occurrences (all)	0	4	2
Cholecystectomy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0

Wisdom teeth removal subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Chills subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Cold sweat subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Drug withdrawal syndrome subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Facial pain subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	4 / 72 (5.56%) 4	2 / 69 (2.90%) 2
Feeling jittery subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Injection site reaction subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Lethargy subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Night sweats subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Nodule			

subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Pyrexia subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Thirst subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Reproductive system and breast disorders Batholin's abscess subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Breast mass subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Breast pain subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Metrorrhagia subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Penis disorder subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Prostatomegaly subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Vaginal haemorrhage			

subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Asthma			
subjects affected / exposed	0 / 72 (0.00%)	3 / 72 (4.17%)	0 / 69 (0.00%)
occurrences (all)	0	3	0
Bronchospasm			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	2 / 69 (2.90%)
occurrences (all)	2	0	2
Chest discomfort			
subjects affected / exposed	3 / 72 (4.17%)	0 / 72 (0.00%)	2 / 69 (2.90%)
occurrences (all)	3	0	2
Chest pain			
subjects affected / exposed	1 / 72 (1.39%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences (all)	1	1	1
Chest tightness			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Chronic rhinosinusitis without nasal polyps			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Cough			
subjects affected / exposed	5 / 72 (6.94%)	3 / 72 (4.17%)	2 / 69 (2.90%)
occurrences (all)	5	3	2
Darker sputum			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Dry throat			

subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Dysphonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences (all)	0	1	2
Dyspnoea			
subjects affected / exposed	1 / 72 (1.39%)	4 / 72 (5.56%)	4 / 69 (5.80%)
occurrences (all)	3	5	5
Epistaxis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Haemoptysis			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	2 / 69 (2.90%)
occurrences (all)	2	0	2
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 72 (0.00%)	3 / 72 (4.17%)	1 / 69 (1.45%)
occurrences (all)	0	3	1
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 72 (1.39%)	2 / 72 (2.78%)	0 / 69 (0.00%)
occurrences (all)	1	2	0
Nasal congestion and inflammation			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Non cardiac chest pain			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	4 / 72 (5.56%)	1 / 72 (1.39%)	2 / 69 (2.90%)
occurrences (all)	4	1	2
Painful respiration			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0

Pulmonary congestion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Pulmonary pain			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Respiratory tract congestion			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Rhinitis allergic			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	1	0	1
Sinus pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Sneezing			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Sputum Increased			
subjects affected / exposed	1 / 72 (1.39%)	2 / 72 (2.78%)	0 / 69 (0.00%)
occurrences (all)	1	2	0
Syncope			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Throat irritation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	1	0	1
Virus			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0

Wheezing subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	2 / 72 (2.78%) 2	3 / 69 (4.35%) 3
Psychiatric disorders			
Anxiety subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Depressed mood subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Nightmare subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Panic attack subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Investigations			
Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Blood abnormal subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Blood urine present subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Colonoscopy subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	2 / 69 (2.90%) 3
Cystoscopy subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Escherichia test positive subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Oesophagogastroduodenoscopy			

subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Serum ferritin decreased			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Weight decreased			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Ankle Fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	1 / 72 (1.39%)	2 / 72 (2.78%)	3 / 69 (4.35%)
occurrences (all)	1	3	3
Head injury			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Ligament sprain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Limb injury			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Pelvic Fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Pulled muscle			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Road traffic accident			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	2
Skin laceration			

subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Cardiac disorders			
Hypertrophic cardiomyopathy subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Arterial fibrosis subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Myocardial infarction subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Tachycardia subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Bundle branch block left subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Palpitations subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Acute coronary syndrome subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Nervous system disorders			
Bell's palsy subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Gait disturbance subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Hypoaesthesia			

subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Loss of consciousness			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Nerve compression			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Ophthalmic migraine			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Taste disorder			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Trigeminal neuralgia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Vertigo positional			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	2 / 69 (2.90%)
occurrences (all)	1	0	2
Lymphadenopathy			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear infection			
subjects affected / exposed	0 / 72 (0.00%)	2 / 72 (2.78%)	0 / 69 (0.00%)
occurrences (all)	0	2	0
Excessive cerumen production			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Otorrhoea			

subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	2 / 69 (2.90%)
occurrences (all)	1	0	2
Eye disorders			
Conjunctivitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Cataract			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Eye Swelling			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	2 / 69 (2.90%)
occurrences (all)	0	0	2
Eye irritation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Eye pruritis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Ocular hyperaemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Swelling of eyelid			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Abdominal distension			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Abdominal pain			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	3	0	1
Abdominal pain upper			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	2	0	1
Anal pruritus			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Appendicitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Chapped lips			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Chest pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Colitis ischaemic			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Constipation			
subjects affected / exposed	1 / 72 (1.39%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	1 / 72 (1.39%)	6 / 72 (8.33%)	3 / 69 (4.35%)
occurrences (all)	1	6	3
Diverticulitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Dry mouth			

subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	2 / 69 (2.90%)
occurrences (all)	2	0	2
Duodenal ulcer perforation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Faeces discoloured			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Gastritis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	1	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Haematochezia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	1	1	0
Haemorrhoids			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Heartburn			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Hernia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Intestinal obstruction			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Irritable bowel syndrome			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Mouth ulceration			

subjects affected / exposed	1 / 72 (1.39%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	1	1	0
Nausea			
subjects affected / exposed	1 / 72 (1.39%)	6 / 72 (8.33%)	7 / 69 (10.14%)
occurrences (all)	1	6	7
Oesophagitis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Oral disorder			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	4 / 72 (5.56%)	2 / 72 (2.78%)	4 / 69 (5.80%)
occurrences (all)	4	2	6
Skin and subcutaneous tissue disorders			
Contusion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Eczema infected			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Flushing			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0

Photodermatosis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 72 (0.00%)	5 / 72 (6.94%)	3 / 69 (4.35%)
occurrences (all)	0	5	3
Skin infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Hernia repair			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Hip surgery			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Limb operation			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	2	0	0
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	0	0	0
Pyelonephritis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Renal mass			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Unstable bladder			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	1 / 69 (1.45%)
occurrences (all)	0	1	1
Urinary Tract Infection			
subjects affected / exposed	0 / 72 (0.00%)	4 / 72 (5.56%)	5 / 69 (7.25%)
occurrences (all)	0	7	8
Endocrine disorders			

Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2	0 / 72 (0.00%) 0	2 / 69 (2.90%) 2
Back pain subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	2 / 72 (2.78%) 2	1 / 69 (1.45%) 1
Fall subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Joint swelling subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	2 / 72 (2.78%) 2	0 / 69 (0.00%) 0
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	1 / 72 (1.39%) 1	1 / 69 (1.45%) 1
Musculoskeletal knee pain subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Neck pain subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	1 / 69 (1.45%) 1
Pain in extremity subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 72 (0.00%) 0	2 / 69 (2.90%) 2
Radius fracture subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0
Spinal stenosis			

subjects affected / exposed occurrences (all)	0 / 72 (0.00%) 0	0 / 72 (0.00%) 0	0 / 69 (0.00%) 0
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Boil			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Candida infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Covid-19			
subjects affected / exposed	3 / 72 (4.17%)	5 / 72 (6.94%)	5 / 69 (7.25%)
occurrences (all)	3	5	5
Escherichia infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Eye infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	2	0	0
Fungal infections			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Furuncle			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Helicobacter infection			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	2	0	1
Hepes zoster			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	2 / 72 (2.78%)	0 / 72 (0.00%)	3 / 69 (4.35%)
occurrences (all)	2	0	3

Kidney infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 72 (1.39%)	1 / 72 (1.39%)	2 / 69 (2.90%)
occurrences (all)	1	1	3
Onychomycosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Parotitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Pseudomonas infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	1	0
Sinus infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	3 / 72 (4.17%)	1 / 72 (1.39%)	2 / 69 (2.90%)
occurrences (all)	9	1	3
Tooth abscess			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	1 / 69 (1.45%)
occurrences (all)	1	0	1
Viral infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 72 (1.39%)	0 / 69 (0.00%)
occurrences (all)	0	2	0

Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	1 / 72 (1.39%)	0 / 72 (0.00%)	0 / 69 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Control: Standard Care		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 71 (57.75%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Large intestine polyp			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Lipoma			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Prostate cancer			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Circulatory collapse			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Haematuria			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pulmonary embolism			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Thrombophlebitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Varicose vein			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Surgical and medical procedures			
Cataract Operation			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Cholecystectomy			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Wisdom teeth removal			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Cold sweat			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Drug withdrawal syndrome			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Facial pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Feeling jittery			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Injection site reaction			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Lethargy			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Night sweats			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nodule			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Urticaria			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Batholin's abscess			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Breast mass			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Breast pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Metrorrhagia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Penis disorder			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Prostatomegaly			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Asthma			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Chest discomfort			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Chest tightness			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Chronic rhinosinusitis without nasal polyps			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Darker sputum			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Dry throat			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Dysphonia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Haemoptysis			

subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Nasal congestion and inflammation			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Non cardiac chest pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Painful respiration			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pulmonary congestion			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pulmonary pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Respiratory tract congestion			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Rhinitis allergic			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Sinus pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Sneezing			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Sputum Increased			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Throat irritation			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Virus			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Wheezing			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Depressed mood			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nightmare			

subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Panic attack			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Blood abnormal			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Blood urine present			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Colonoscopy			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Cystoscopy			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Escherichia test positive			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Oesophagogastroduodenoscopy			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Serum ferritin decreased			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			

Ankle Fracture			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Fall			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Head injury			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Ligament sprain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pelvic Fracture			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Pulled muscle			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Road traffic accident			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Skin laceration			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Arterial fibrosis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Myocardial infarction			

subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Tachycardia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Bundle branch block left			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Palpitations			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Acute coronary syndrome			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Atrial fibrillation			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Bell's palsy			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Gait disturbance			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Loss of consciousness			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nerve compression			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Ophthalmic migraine			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Taste disorder subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Trigeminal neuralgia subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Vertigo positional subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Lymphadenopathy subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Ear and labyrinth disorders Ear infection subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Excessive cerumen production subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Otorrhoea subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Tinnitus subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Vertigo subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	0 / 71 (0.00%) 0		
Cataract			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Eye Swelling			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Eye irritation			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Eye pruritis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Ocular hyperaemia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Swelling of eyelid			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Anal pruritus			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Appendicitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Chapped lips			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Colitis ischaemic			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	4		
Diverticulitis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Duodenal ulcer perforation			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Faeces discoloured			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Heartburn			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hernia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Intestinal obstruction			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Irritable bowel syndrome			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Oesophagitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Oral disorder			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Vomiting			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Contusion			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Eczema infected			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Flushing			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Nail disorder			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Photodermatitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Skin infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hernia repair			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hip surgery			

subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Limb operation			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Pyelonephritis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Renal mass			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Unstable bladder			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Urinary Tract Infection			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Endocrine disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	3		
Fall			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Joint swelling			

subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	2		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Musculoskeletal knee pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Radius fracture			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Spinal stenosis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Boil			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Candida infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Covid-19			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		

Escherichia infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Eye infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Fungal infections			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Furuncle			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Helicobacter infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Hepes zoster			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Kidney infection			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	3 / 71 (4.23%)		
occurrences (all)	3		
Onychomycosis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Parotitis			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

Pseudomonas infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Sinus infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Tooth abscess			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences (all)	2		
Viral infection			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 71 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2018	Addition of a new site: University Hospitals of Morecombe Bay NHS Foundation Trust – Royal Lancaster Infirmary
26 March 2018	<ol style="list-style-type: none"> 1. Protocol, patient information sheet, RSSQ_since last visit, RSSQ_symptoms of exacerbation, RSSQ_end of exacerbation, and GP letter updated to remove aspects of examiner blinding 2. Protocol amended to include more information on DRA, exacerbation management and re-order the inclusion.exclusion criteria 3. PIS to include the DRA and instructions re management of exacerbation 4. Informed consent changed to reflect the change in version of the PIS 5. Inclusion of the Ethics Reference Number
22 August 2018	Application updated to include a new site: Southern Health & Social Care Trust_Craigavon Area Hospital
25 February 2019	Application updated to include a new site: North Tees and Hartlepool NHS Foundation Trust_North Tees University Hospital
12 March 2019	Addition of a participant Newsletter
29 August 2019	<p>eporting section to remove the timeline and that these will be reported to CTU.</p> <ol style="list-style-type: none"> 2. Updates to the current versions of the Patient Information Sheet and consent form: <ul style="list-style-type: none"> • Cover sheet page numbers corrected. • Add information about addition of spirometry sub-study • Add information about requirement for salbutamol during study being assessed by study doctor. • Addition to calendar lung function at home on day of study visit. • Removal of information about prescription data being reviewed from information sheet and consent form. • Addition of a standalone Data Transparency Statement with an accompanying cover letter. 3. Update to the GP Letter to allow sites to highlight that a Drug Response Assessment will be completed for patients allocated to the MucoClear treatment groups and to allow the inclusion of text about the patient being prescribed a bronchodilator if required.
14 October 2019	Update to application to add the following site: Imperial College Healthcare NHS Trust_St Mary's Hospital
14 November 2019	Update to application to add the following site: County Durham and Darlington Foundation Trust_Darlington Memorial Hospital
13 February 2020	Update to application to add the following sites: <ul style="list-style-type: none"> • Blackpool Teaching Hospitals NHS Foundation Trust_Blackpool Victoria Hospital, with PI Dr Tarek Saba • NHS Great Glasgow and Clyde_Glasgow Royal Infirmary, with PI Dr Eric Livingstone

27 March 2020	Update to application to add the following sites: > Bradford Teaching Hospitals NHS Foundation Trust _Bradford Royal Infirmary > Swansea Bay University Health Board_Morriston Hospital Swansea > Northumbria Healthcare NHS Foundation Trust_North Tyneside General Hospital
13 May 2020	Update to application to add the following sites: • Stoke Mandeville Hospital, Buckinghamshire Healthcare NHS Trust, with PI Dr Mitra Shahidi
14 July 2020	A Belfast team, as representatives of the CI/QUB team, can support CLEAR trial sites across the UK to deliver follow-up visits by phone if local site resources are unable to deliver.
13 October 2021	Extension to study recruitment until September 2022, reduction in sample size (288) to 80% power, removal of 2nd year follow up - leaving a 12-month study period, update of inclusion criteria from "Two or more pulmonary exacerbations in the last year requiring antibiotics to " Two or more pulmonary exacerbations in a 1 year period in the past 2 years requiring antibiotics"
27 October 2021	Update to Mucodyne SPC & Mucoclear Info Leaflet
17 December 2021	Addition of Patient Information Sheet/Consent Form document for the CLEAR EME Sputum Sample Sub-study.
03 August 2022	<ul style="list-style-type: none"> • A Change to inclusion criteria - Changed from "2 or more pulmonary exacerbations in a 1 year period in the past 2 years requiring antibiotics" to "One or more pulmonary exacerbations in the last year requiring antibiotics. • The removal of SWATs A and B • The addition of the collection of data from patient's electronic records at 104 weeks post randomisation (for patients recruited prior to the implementation of protocol v5.0) • Removal of the stipulation of 14 EME sites (to have no limit on the number of EME sites) • 3 G.P surgeries to be added as P.I.C. sites within the primary care setting

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
12 March 2020	Pause to recruitment due to Covid-19 pandemic.	01 November 2021

Notes:

Limitations and caveats

None reported