



Clinical trial results:

A randomised, double-blind placebo controlled trial of the effectiveness of low dose oral theophylline as an adjunct to inhaled corticosteroids in preventing exacerbations of chronic obstructive pulmonary disease

Summary

EudraCT number	2013-001490-25
Trial protocol	GB
Global end of trial date	06 September 2017

Results information

Result version number	v1 (current)
This version publication date	11 December 2020
First version publication date	11 December 2020

Trial information

Trial identification

Sponsor protocol code	3/016/13
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Additional study identifiers

ISRCTN number	ISRCTN27066620
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Aberdeen
Sponsor organisation address	Foresterhill, Aberdeen, United Kingdom, AB25 2ZD
Public contact	Seonaidh Cotton, University of Aberdeen, 44 01224438178, s.c.cotton@abdn.ac.uk
Scientific contact	Seonaidh Cotton, University of Aberdeen, 44 01224438178, s.c.cotton@abdn.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	22 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 September 2017
Global end of trial reached?	Yes
Global end of trial date	06 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine whether adding low-dose theophylline to existing treatment (inhaled corticosteroid therapy) in patients who have chronic obstructive pulmonary disease will reduce the number of exacerbations (or flare-ups) of the condition. If the treatment is effective, we will also assess whether it is cost effective.

Protection of trial subjects:

Patients had 24 hour / day contact number for study team

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2013
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: 1567
Worldwide total number of subjects	1567
EEA total number of subjects	1567

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)	471
From 65 to 84 years	1068
85 years and over	28

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1648 screened, 62 were not eligible, 8 eligible but did not consent, 1578 randomised, but 11 excluded post-randomisation, so 1567 included in study for baseline

Period 1

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

Arms

Are arms mutually exclusive? Yes

Arm title Placebo

Arm description: -

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:

Twice a day for 52 weeks

Arm title Theophylline

Arm description: -

Arm type Experimental

Investigational medicinal product name uniphyllin

Investigational medicinal product code

Other name

Pharmaceutical forms Tablet

Routes of administration Oral use

Dosage and administration details:

Uniphyllin MR 200 mg tablets taken once or twice a day for 52 weeks

Number of subjects in period 1	Placebo	Theophylline
Started	779	788
Completed	764	772
Not completed	15	16
Lost to follow-up	15	16

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Theophylline
Reporting group description: -	

Reporting group values	Placebo	Theophylline	Total
Number of subjects	779	788	1567
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	68.5	68.3	
standard deviation	± 8.6	± 8.2	-
Gender categorical Units: Subjects			
Female	361	363	724
Male	418	425	843

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Theophylline
Reporting group description: -	

Primary: Number of exacerbations

End point title	Number of exacerbations
End point description:	
End point type	Primary
End point timeframe:	
Number of exacerbations during 12 months of follow-up	

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	764	772		
Units: number	764	772		

Statistical analyses

Statistical analysis title	Negative binomial for primary outcome
Statistical analysis description:	
The primary outcome (number of COPD exacerbations requiring antibiotics and/or oral corticosteroids in the 12 month treatment period following randomisation) was compared between randomised groups using a generalised linear model with log-link function, over dispersion parameter and length of time in study as an offset. The estimated treatment effect is presented as unadjusted rate ratio followed by adjusted rate ratio for a set of pre-specified baseline variables. The adjustment variables were	
Comparison groups	Placebo v Theophylline
Number of subjects included in analysis	1536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Negative binomial model
Parameter estimate	Risk ratio (RR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.08

Secondary: COPD hospital admissions

End point title	COPD hospital admissions
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End point description:

Number of hospital admissions for COPD related reasons between randomisation and 12 months follow-up

End point type	Secondary
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End point timeframe:

Between randomisation and 12 months post randomisation.

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	764	772		
Units: number	764	772		

Statistical analyses

Statistical analysis title	Secondary outcome: COPD hospital admission
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Statistical analysis description:

Negative binomial model for outcome number of hospital admissions for COPD. Model offset by time in study, and model adjusted for covariates listed for primary outcome.

Comparison groups	Placebo v Theophylline
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Number of subjects included in analysis	1536
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.02
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Method	Negative binomial model
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Parameter estimate	Risk ratio (RR)
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Point estimate	0.72
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.55
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upper limit	0.94
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Secondary: Non-COPD hospital admissions

End point title	Non-COPD hospital admissions
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End point description:

End point type	Secondary
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End point timeframe:

From randomisation to 12 months post randomisation

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	755	762		
Units: Number	755	762		

Statistical analyses

Statistical analysis title	Non-COPD hospital admissions
Comparison groups	Placebo v Theophylline
Number of subjects included in analysis	1517
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.38

Secondary: FEV1 % predicted

End point title	FEV1 % predicted
End point description:	
End point type	Secondary
End point timeframe:	
FEV1 measured at baseline, 26 and 52 weeks followup.	

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	761	771		
Units: % predicted FEV1 (volume per second)				
least squares mean (standard error)	55.81 (± 2.62)	55.25 (± 2.64)		

Statistical analyses

Statistical analysis title	FEV1% predicted
Statistical analysis description: Mixed effect models used to compare FEV1 % predicted between placebo and theophylline	
Comparison groups	Placebo v Theophylline
Number of subjects included in analysis	1532
Analysis specification	Pre-specified
Analysis type	other
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.42
upper limit	1.3

Secondary: COPD assessment test (CAT)

End point title	COPD assessment test (CAT)
End point description:	
End point type	Secondary
End point timeframe: Measured baseline, 26 and 52 weeks.	

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	760	772		
Units: Score 0 to 40				
arithmetic mean (standard error)	21.20 (\pm 1.07)	21.21 (\pm 1.07)		

Statistical analyses

Statistical analysis title	Secondary outcome: CAT score
Statistical analysis description: mixed model of CAT score as outcome,	
Comparison groups	Placebo v Theophylline

Number of subjects included in analysis	1532
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.975
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.68

Secondary: mMRC dyspnea score

End point title	mMRC dyspnea score
End point description:	
End point type	Secondary
End point timeframe:	
Collected at baseline, 26 and 52 weeks	

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	615	631		
Units: score 0 to 4				
number (not applicable)				
0: Breathless on strenuous exercise	52	38		
1: Breathless hurrying	158	186		
2: Slower than contemporaries	182	174		
3: Stop after 100m	167	178		
4: Breathless after leaving house	56	55		

Statistical analyses

Statistical analysis title	mMRC dyspnea score
Statistical analysis description:	
Chi-squared test between score and treatment group	
Comparison groups	Placebo v Theophylline

Number of subjects included in analysis	1246
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.31
Method	Chi-squared

Notes:

[1] - Chi-squared on difference at 52 weeks

Secondary: Pneumonia

End point title	Pneumonia
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End point description:

End point type	Secondary
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End point timeframe:

Binary variable indicating whether at pneumonia during the 12 month follow-up period.

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	764	772		
Units: number of participants	9	14		

Statistical analyses

Statistical analysis title	Pneumonia
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Statistical analysis description:

Mixed effects logistic model, unadjusted estimates due to small event count

Comparison groups	Placebo v Theophylline
Number of subjects included in analysis	1536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307
Method	Mixed models analysis
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	3.62

Secondary: All-cause mortality

End point title	All-cause mortality
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End point description:

End point type	Secondary
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End point timeframe:

Count of number of people who die during the 12 month follow-up

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	764	772		
Units: Number of participants dying	14	19		

Statistical analyses

Statistical analysis title	All_cause mortality
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Statistical analysis description:

Cox regression model, unadjusted

Comparison groups	Placebo v Theophylline
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Number of subjects included in analysis	1536
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.398
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Method	Regression, Cox
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Parameter estimate	Hazard ratio (HR)
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Point estimate	1.35
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.68
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upper limit	2.69
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Secondary: COPD related mortality

End point title	COPD related mortality
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End point description:

End point type	Secondary
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End point timeframe:

During the 12 months follow-up

End point values	Placebo	Theophylline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	764	772		
Units: Number dead with COPD reasons	8	7		

Statistical analyses

Statistical analysis title	COPD related mortality
Statistical analysis description:	
Cox regression	
Comparison groups	Placebo v Theophylline
Number of subjects included in analysis	1536
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.785
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	2.07

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

12 months of trial participation

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Theophylline
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Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The side effect profile of theophylline is well established (has been used for 80 years), collection of AE data would not add to the scientific body of knowledge and could not justify the resources required to collect these data

Serious adverse events	Placebo	Theophylline	
Total subjects affected by serious adverse events			
subjects affected / exposed	108 / 770 (14.03%)	103 / 783 (13.15%)	
number of deaths (all causes)	14	19	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 770 (0.00%)	3 / 783 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoid tumour of the caecum			

subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic cancer metastatic			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	3 / 770 (0.39%)	7 / 783 (0.89%)	
occurrences causally related to treatment / all	0 / 3	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	1 / 770 (0.13%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			

subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 770 (0.00%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebral haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	2 / 770 (0.26%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 770 (0.13%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	1 / 770 (0.13%)	13 / 783 (1.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular occlusion			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Carotid endarterectomy			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethrotomy			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 770 (0.39%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site pain			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Malaise			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Chest pain			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	2 / 770 (0.26%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 770 (0.65%)	4 / 783 (0.51%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 5	0 / 2	
Haemoptysis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			

subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxia		
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	2 / 770 (0.26%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1
Pleural effusion		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pleurisy		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pleuritic pain		
subjects affected / exposed	0 / 770 (0.00%)	3 / 783 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia aspiration		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Pneumothorax		
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary embolism		

subjects affected / exposed	3 / 770 (0.39%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	3 / 770 (0.39%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 770 (0.00%)	103 / 783 (13.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood calcium			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural			

complications			
Accidental death			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acetabulum fracture			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	2 / 770 (0.26%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	5 / 770 (0.65%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	2 / 770 (0.26%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			

subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Multiple fractures		
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Postoperative wound infection		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Prescribed overdose		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Procedural vomiting		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rib fracture		
subjects affected / exposed	3 / 770 (0.39%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Substance-induced psychotic disorder		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tibia fracture		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ulna fracture		

subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	3 / 770 (0.39%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	2 / 770 (0.26%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 770 (0.26%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	4 / 770 (0.52%)	13 / 783 (1.66%)
occurrences causally related to treatment / all	0 / 4	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Atrial tachycardia		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block		
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac arrest		
subjects affected / exposed	2 / 770 (0.26%)	3 / 783 (0.38%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 3
Cardiac failure		
subjects affected / exposed	3 / 770 (0.39%)	2 / 783 (0.26%)
occurrences causally related to treatment / all	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
chest pain		
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Left ventricular failure		
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial infarction		
subjects affected / exposed	2 / 770 (0.26%)	0 / 783 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Palpitations		

subjects affected / exposed	2 / 770 (0.26%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 770 (0.00%)	103 / 783 (13.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 770 (0.00%)	13 / 783 (1.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 770 (0.00%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 770 (0.00%)	103 / 783 (13.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			

subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 770 (0.13%)	3 / 783 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Frontotemporal dementia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 770 (0.00%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 770 (0.00%)	13 / 783 (1.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 770 (0.00%)	4 / 783 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	0 / 770 (0.00%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	2 / 770 (0.26%)	3 / 783 (0.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 770 (0.26%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 770 (0.00%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematemesis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 770 (0.00%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			

subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary sepsis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 770 (0.00%)	103 / 783 (13.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 770 (0.13%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genitourinary tract infection			
subjects affected / exposed	0 / 770 (0.00%)	2 / 783 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 770 (0.00%)	3 / 783 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal stiffness			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			

subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Arthritis infective			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blister infected			
subjects affected / exposed	1 / 770 (0.13%)	0 / 783 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 770 (0.13%)	5 / 783 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periumbilical abscess			
subjects affected / exposed	0 / 770 (0.00%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 770 (0.39%)	1 / 783 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 770 (0.13%)	4 / 783 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Refeeding syndrome			
subjects affected / exposed	0 / 770 (0.00%)	13 / 783 (1.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Theophylline	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 770 (0.00%)	0 / 783 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30326124>