



Clinical trial results:

A randomised phase III placebo-controlled trial evaluating the addition of celecoxib to standard treatment of transitional cell carcinoma of the bladder

Summary

EudraCT number	2006-000687-89
Trial protocol	GB
Global end of trial date	02 November 2020

Results information

Result version number	v1 (current)
This version publication date	13 November 2021
First version publication date	13 November 2021

Trial information

Trial identification

Sponsor protocol code	ICR-CTSU/2008/10018
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Additional study identifiers

ISRCTN number	ISRCTN84681538
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Sponsor Identification Number:: CCR2732, REC reference:: 06/Q0104/57, IRAS ID:: 32582, Protocol code no:: UR0601

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	15 Cotswold Road, London, United Kingdom, SM2 5NG
Public contact	Steven Penegar, The Institute of Cancer Research, 44 2087224238, boxit-icrctsu@icr.ac.uk
Scientific contact	Steven Penegar, The Institute of Cancer Research, 44 2087224238, boxit-icrctsu@icr.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	10 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 November 2020
Global end of trial reached?	Yes
Global end of trial date	02 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To determine if the addition of the oral COX-2 inhibitor celecoxib to standard therapy is more effective in terms of disease recurrence at 3 years than standard therapy alone for the treatment of superficial TCC of the bladder at high risk of recurrence.
2. To determine if the addition of the oral COX-2 inhibitor celecoxib to standard therapy is more effective in terms of disease recurrence at 3 years than standard therapy alone for the treatment of superficial TCC of the bladder at intermediate risk of recurrence.

Protection of trial subjects:

For trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.

Eligible patients were given as much time as they needed to consider and come to a decision about entering the trial, prior to giving consent for registration. The patient information sheet, described fully which parties would have access to their identifiable personal information and patients were asked to give consent to this.

The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy:

Bladder cancer represents the ninth most common cancer with 429 000 newcases per year worldwide. Over 75% of new cases are non-muscle-invasive bladder cancer (NMIBC), and following tumour resection, 28–52% of patients develop recurrence within 5 yr. Efforts to reduce recurrence of NMIBC include the use of intravesical chemotherapy and bacillus Calmette-Guérin (BCG)

Evidence for comparator:

Cyclo-oxygenase (COX) enzyme controls a rate-limiting step implicated in carcinogenesis by regulating the conversion of arachidonic acid to prostaglandin E2 (PGE2) and inhibits apoptosis by overexpressing Bcl-2. COX-2 inhibition results in cell cycle arrest, triggering apoptosis in in vitro studies. A population-based case-controlled study reported that patients taking regular nonsteroidal anti-inflammatory drugs (NSAIDs) had a lower risk of developing bladder cancer (odds ratio 0.81, 95% confidence interval [CI]: 0.68–0.96) compared with patients with nonor irregular NSAID use. Consistent with this, COX-2 is overexpressed in bladder cancer compared with normal urothelium, and COX-2 expression is associated with disease recurrence and progression.

Actual start date of recruitment	31 July 2007
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: 472
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Worldwide total number of subjects	472
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)	194
From 65 to 84 years	270
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Between 1 November 2007 and 23 July 2012, 472 patients (236 celecoxib, 236 placebo) were recruited from 51 centres in the UK.

At end of trial (2 November 2020), median follow-up was 65.4 months (Q1 51.5m to Q3 78.9m). The principal analysis of the primary endpoint was done after a median follow-up of 42.6m and published in 2019 (see links below).

Pre-assignment

Screening details:

Patients that met the eligibility criteria were recruited into the study.

Period 1

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

Blinding implementation details:

Following TURBT, randomisation was performed by telephone. Treatment was then allocated (1:1) using computer-generated random permuted blocks of size 6, stratified by treating centre and risk group. Treatment allocation was blinded to participants and investigators. The IDMC reviewed safety and efficacy of the trial blinded to treatment allocation. A cardiovascular safety committee (CVSC) was established to review unblinded CV safety data to advise in confidence the IDMC.

Arms

Are arms mutually exclusive?	Yes
Arm title	Celecoxib

Arm description:

Patients were randomised to celecoxib 200 mg twice daily for 2 yr.

Arm type	Experimental
Investigational medicinal product name	Celecoxib 200 mg twice daily
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

It was recommended that all patients received standard-of-care single intravesical 40 mg in 40 ml of mitomycin C (MMC1) instillation within 24 h following TURBT unless contraindicated. High risk patients received induction BCG (81 mg BCG, Connaught strain) comprising six weekly instillations, and maintenance therapy (three weekly instillations at 4, 6, 12, 18, 24, 30, and 36 mo) was recommended. Study treatment was commenced before BCG induction in high-risk patients. It was recommended that intermediate-risk patients received six weekly instillations of 40 mg MMC (MMC6). Disease recurrence was monitored by regular cystoscopies as per guidelines [3]. Centrally reviewed baseline electrocardiography (ECG) was performed to confirm eligibility, with follow-up ECGs at 12 and 24 mo.

Arm title	Placebo
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Arm description:

Patients were randomised to placebo twice daily for 2 yr.

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

Dosage and administration details:

2 tablets per day

Number of subjects in period 1	Celecoxib	Placebo
Started	236	236
Completed	224	213
Not completed	12	23
Consent withdrawn by subject	5	12
Lost to follow-up	4	8
Protocol deviation	3	3

Baseline characteristics

Reporting groups

Reporting group title	Celecoxib
Reporting group description:	
Patients were randomised to celecoxib 200 mg twice daily for 2 yr.	
Reporting group title	Placebo
Reporting group description:	
Patients were randomised to placebo twice daily for 2 yr.	

Reporting group values	Celecoxib	Placebo	Total
Number of subjects	236	236	472
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	65.8	67.1	
standard deviation	± 10.9	± 8.8	-
Gender categorical			
Units: Subjects			
Female	48	50	98
Male	188	186	374
Risk group			
NMIBC risk categorisation according to European Association of Urology guidelines (2002)			
Units: Subjects			
Intermediate	167	179	346
High	69	57	126

End points

End points reporting groups

Reporting group title	Celecoxib
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Reporting group description:

Patients were randomised to celecoxib 200 mg twice daily for 2 yr.

Reporting group title	Placebo
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Reporting group description:

Patients were randomised to placebo twice daily for 2 yr.

Subject analysis set title	Celecoxib - Per protocol population
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Subject analysis set type	Per protocol
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Subject analysis set description:

This population contains all randomised patients who received at least 12 months of allocated study drug. Patients who received at least one dose of the allocated study drug and who stopped treatment early for reasons mandated within the protocol will also be included. Patients receiving less than 12 months of treatment for reasons not mandated in the protocol and patients with other major protocol violations will be excluded. No differences between reasons for non-compliance early in the two treatment groups were detected.

Subject analysis set title	Placebo - Per protocol population
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Subject analysis set type	Per protocol
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Subject analysis set description:

This population contains all randomised patients who received at least 12 months of allocated study drug. Patients who received at least one dose of the allocated study drug and who stopped treatment early for reasons mandated within the protocol will also be included. Patients receiving less than 12 months of treatment for reasons not mandated in the protocol and patients with other major protocol violations will be excluded. No differences between reasons for non-compliance early in the two treatment groups were detected.

Primary: Time to recurrence of transitional cell carcinoma of the bladder

End point title	Time to recurrence of transitional cell carcinoma of the bladder
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End point description:

Time to recurrence is defined as the time from randomisation to the first disease recurrence, defined as recurrence of NMIBC or progression to invasive disease in the bladder. Patients alive and recurrence free at the time of analysis and patients lost to follow-up are censored at last available assessment; patients with distant metastatic recurrence or bladder cancer death without prior loco-regional recurrence, or patients with second primaries were censored at the date of the event. Patients who died due to other causes were censored at the time of death.

End point type	Primary
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End point timeframe:

Three years post randomisation

End point values	Celecoxib	Placebo	Celecoxib - Per protocol population	Placebo - Per protocol population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	236	236	211	217
Units: Percentage free of event				
number (confidence interval 95%)	67.7 (61.2 to 73.4)	63.9 (57.1 to 69.8)	67.1 (60.2 to 73.0)	62.7 (55.7 to 68.9)

Statistical analyses

Statistical analysis title	Main analysis primary endpoint
Statistical analysis description: Percentage free of event is estimated by Kaplan-Meier and the stratified logrank test is used to test for differences between the two groups, accounting for differences in risk groups. The magnitude of treatment effect is estimated using a Cox regression model stratified by risk group. Hazard ratios <1 indicate a benefit in the Celecoxib group throughout.	
Comparison groups	Placebo v Celecoxib
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.28 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.15

Notes:

[1] - Log rank stratified by risk group

Statistical analysis title	Sensitivity analysis - PP population
Statistical analysis description: Repeat main analysis on the PP population	
Comparison groups	Placebo - Per protocol population v Celecoxib - Per protocol population
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.14

Secondary: Recurrence Rate

End point title	Recurrence Rate
End point description: Recurrence rate was analysed in the intermediate risk group only, as patients in the high risk group are usually expected to come off study treatment at first recurrence. Recurrence rate is calculated as the number of non-muscle invasive recurrences in the study period divided by the length of the study period. Any NMIBC reported on the same date that the study period ends (e.g. when NMIBC and MIBC are reported at the same visit) are included in the total number of recurrences.	
End point type	Secondary

End point timeframe:

The study period is defined as time from randomisation to first of invasive or metastatic recurrence, death or censoring as for the primary endpoint.

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	57		
Units: recurrence/patient				
median (inter-quartile range (Q1-Q3))	0 (0 to 2)	1 (0 to 2)		

Statistical analyses

Statistical analysis title	Main analysis recurrence rate
Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	126
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Wilcoxon (Mann-Whitney)

Secondary: Recurrence rate at 3 months

End point title	Recurrence rate at 3 months
End point description:	The recurrence rate at 3 months calculated using Kaplan-Meier methods.
End point type	Secondary
End point timeframe:	3 months

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: Percentage with event by 3 months				
number (confidence interval 95%)	6.1 (3.6 to 10)	7.8 (5.0 to 12.1)		

Statistical analyses

Secondary: Time to progression to invasive disease of the bladder (high risk patients only)

End point title	Time to progression to invasive disease of the bladder (high risk patients only)
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End point description:

Time to progression to invasive disease of the bladder is defined, in high risk patients only, as the time from randomisation to the first of increase to stage T2 or higher disease in the bladder or metastatic disease.

- Patients without a prior progression to invasive disease of the bladder or metastatic disease are censored at time of second primary outside the bladder or prostate (second primary cancers of the prostate are ignored or censored as in the primary endpoint).
- In the absence of a separate report of progression or metastasis, if a patient is reported as dying from bladder cancer; a progression is assumed at the date of death.
- Patients not experiencing any of these events will be censored at death from any other cause or last known follow-up.

End point type	Secondary
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End point timeframe:

3 years

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167	179		
Units: Percentage free of event				
number (confidence interval 95%)	89 (83 to 93.1)	90.4 (84.8 to 94)		

Statistical analyses

Statistical analysis title	Main analysis time to progression
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Statistical analysis description:

Percentage free of event is estimated using Kaplan-Meier, and the logrank test is used to test for differences between the two groups. The magnitude of treatment effect is estimated using a Cox regression model. Hazard ratios <1 indicate a benefit in the Celecoxib group throughout.

Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.96

Secondary: Disease Free Survival

End point title	Disease Free Survival
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End point description:

Disease-free survival is defined as time from randomisation to the first of non-muscle invasive recurrence, progression to invasive or metastatic disease, second primary in the bladder or bladder cancer death.

- Bladder cancer death is defined as a death from unknown cause or other death with cause cited as bladder cancer.
- Patients alive and disease free at the time of analysis and patients lost to follow-up will be censored at last available assessment.
- Patients who have been diagnosed with a second primary outside the bladder or prostate will be censored at the date of second primary diagnosis (second primary cancers of the prostate will be ignored or censored as in the primary endpoint).
- Patients dying from other causes without prior recurrence will be censored at date of death.

End point type	Secondary
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End point timeframe:

3 years

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: Percentage free of event				
number (confidence interval 95%)	67.7 (61.2 to 73.4)	63.9 (57.1 to 69.8)		

Statistical analyses

Statistical analysis title	Main analysis DFS
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Statistical analysis description:

Percentage free of event is estimated by Kaplan-Meier and the stratified logrank test is used to test for differences between the two groups, accounting for differences in risk groups. The magnitude of treatment effect is estimated using a Cox regression model stratified by risk group. Hazard ratios <1 indicate a benefit in the Celecoxib group throughout.

Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.12

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

Overall survival is defined as the time from randomisation to death from any cause. Patients lost to follow-up and alive at the time of analysis will be censored at last known follow-up.

End point type	Secondary
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End point timeframe:

5 years

End point values	Celecoxib	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	236	236		
Units: Percentage free of event				
number (confidence interval 95%)	86 (80.6 to 89.9)	88.9 (83.8 to 92.5)		

Statistical analyses

Statistical analysis title	Main analysis OS
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Statistical analysis description:

Percentage free of event is estimated by Kaplan-Meier and the stratified logrank test is used to test for differences between the two groups, accounting for differences in risk groups. The magnitude of treatment effect is estimated using a Cox regression model stratified by risk group. Hazard ratios <1 indicate a benefit in the Celecoxib group throughout.

Comparison groups	Celecoxib v Placebo
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.36
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.04

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation up to 30 days after treatment discontinuation

Adverse event reporting additional description:

Pre-specified toxicities collected at every visit were Insomnia, Rash, Diarrhoea, Flatulence, Dyspepsia, Rhinitis, Pharyngitis, Sinusitis, Upper respiratory tract infection, Oedema peripheral, Dizziness, Abdominal pain. Other toxicities were collected as reported. Non-serious toxicities include serious and non-serious.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	14.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Celecoxib
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Reporting group description: -

Serious adverse events	Placebo	Celecoxib	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 233 (13.73%)	38 / 233 (16.31%)	
number of deaths (all causes)	29	38	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to liver	Additional description: Metastases to liver		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colon cancer stage IV	Additional description: Colon cancer stage IV		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer recurrent	Additional description: Bladder cancer recurrent		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Haemorrhagic stroke	Additional description: Haemorrhagic stroke		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wegener's granulomatosis	Additional description: Wegener's granulomatosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (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			
Transurethral prostatectomy	Additional description: Transurethral prostatectomy		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suprapubic pain	Additional description: Suprapubic pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral	Additional description: Oedema peripheral		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: Pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain	Additional description: Chest pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity	Additional description: Hypersensitivity		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary haemorrhage	Additional description: Pulmonary haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 233 (1.29%)	4 / 233 (1.72%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pleural effusion	Additional description: Pleural effusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm	Additional description: Bronchospasm		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough	Additional description: Cough		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 233 (0.86%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration	Additional description: Aspiration		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state	Additional description: Confusional state		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Haemoglobin	Additional description: Haemoglobin		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerular filtration rate decreased	Additional description: Glomerular filtration rate decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased	Additional description: Weight decreased		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture	Additional description: Ankle fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chemical cystitis	Additional description: Chemical cystitis		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence	Additional description: Wound dehiscence		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation	Additional description: Joint dislocation		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion	Additional description: Contusion		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture	Additional description: Wrist fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture	Additional description: Femur fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture	Additional description: Tibia fracture		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Tachycardia	Additional description: Tachycardia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation	Additional description: Atrial fibrillation		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 233 (0.86%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia	Additional description: Myocardial ischaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations	Additional description: Palpitations		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome	Additional description: Acute coronary syndrome		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete	Additional description: Atrioventricular block complete		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction	Additional description: Myocardial infarction		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 233 (0.00%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure	Additional description: Left ventricular failure		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction	Additional description: Acute myocardial infarction		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris	Additional description: Angina pectoris		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache	Additional description: Headache		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory loss	Additional description: Sensory loss		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor	Additional description: Tremor		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis	Additional description: IIIrd nerve paralysis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy	Additional description: Lethargy		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope	Additional description: Presyncope		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia	Additional description: Aphasia		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: Dizziness		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye inflammation	Additional description: Eye inflammation		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage	Additional description: Eye haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iris adhesions	Additional description: Iris adhesions		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation	Additional description: Constipation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction	Additional description: Small intestinal obstruction		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena	Additional description: Melaena		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper	Additional description: Abdominal pain upper		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis	Additional description: Gastritis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage	Additional description: Gastrointestinal haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation	Additional description: Intestinal perforation		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectal haemorrhage	Additional description: Rectal haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Abdominal pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis	Additional description: Cholangitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis	Additional description: Cholelithiasis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (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	Additional description: Rash		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary bladder haemorrhage	Additional description: Urinary bladder haemorrhage		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment	Additional description: Renal impairment		

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder pain	Additional description: Bladder pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention	Additional description: Urinary retention		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 233 (0.86%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis	Additional description: Hydronephrosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure	Additional description: Renal failure		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pollakiuria	Additional description: Pollakiuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria	Additional description: Dysuria		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria	Additional description: Haematuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 233 (2.58%)	3 / 233 (1.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia	Additional description: Arthralgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain	Additional description: Bone pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arthritis	Additional description: Arthritis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain	Additional description: Groin pain		
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations	Additional description: Pneumonia		
Pneumonia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 233 (0.86%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis	Additional description: Urosepsis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection	Additional description: Febrile infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 233 (0.86%)	2 / 233 (0.86%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis	Additional description: Endocarditis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis	Additional description: Appendicitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis	Additional description: Diverticulitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 233 (0.00%)	1 / 233 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis	Additional description: Necrotising fasciitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite	Additional description: Decreased appetite		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia	Additional description: Hyperglycaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia	Additional description: Hypercalcaemia		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 233 (0.43%)	0 / 233 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Celecoxib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	183 / 233 (78.54%)	188 / 233 (80.69%)	
Nervous system disorders			
Dizziness	Additional description: Dizziness		
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 233 (11.59%)	39 / 233 (16.74%)	
occurrences (all)	58	79	
General disorders and administration site conditions			
Oedema peripheral	Additional description: Oedema peripheral		
alternative assessment type: Non-systematic			
subjects affected / exposed	23 / 233 (9.87%)	24 / 233 (10.30%)	
occurrences (all)	50	56	
Fatigue	Additional description: Fatigue		
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 233 (9.44%)	27 / 233 (11.59%)	
occurrences (all)	31	50	
Gastrointestinal disorders			

Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Diarrhoea		
	33 / 233 (14.16%)	41 / 233 (17.60%)	
	52	72	
Flatulence alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Flatulence		
	71 / 233 (30.47%)	64 / 233 (27.47%)	
	185	172	
Abdominal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Abdominal pain		
	40 / 233 (17.17%)	51 / 233 (21.89%)	
	71	83	
Constipation alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Constipation		
	15 / 233 (6.44%)	14 / 233 (6.01%)	
	21	28	
Dyspepsia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Dyspepsia		
	64 / 233 (27.47%)	78 / 233 (33.48%)	
	120	172	
Skin and subcutaneous tissue disorders Rash alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Rash		
	32 / 233 (13.73%)	31 / 233 (13.30%)	
	54	50	
Psychiatric disorders Insomnia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	Additional description: Insomnia		
	52 / 233 (22.32%)	52 / 233 (22.32%)	
	123	105	
Renal and urinary disorders Haematuria alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Dysuria	Additional description: Haematuria		
	22 / 233 (9.44%)	18 / 233 (7.73%)	
	31	24	
	Additional description: Dysuria		

alternative assessment type: Non-systematic			
subjects affected / exposed	31 / 233 (13.30%)	23 / 233 (9.87%)	
occurrences (all)	52	44	
Micturition urgency	Additional description: Micturition urgency		
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 233 (11.59%)	18 / 233 (7.73%)	
occurrences (all)	62	32	
Pollakiuria	Additional description: Pollakiuria		
alternative assessment type: Non-systematic			
subjects affected / exposed	46 / 233 (19.74%)	39 / 233 (16.74%)	
occurrences (all)	105	79	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 233 (5.58%)	14 / 233 (6.01%)	
occurrences (all)	19	26	
Arthralgia	Additional description: Arthralgia		
alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 233 (5.58%)	13 / 233 (5.58%)	
occurrences (all)	22	18	
Infections and infestations			
Urinary tract infection	Additional description: Urinary tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 233 (7.30%)	18 / 233 (7.73%)	
occurrences (all)	21	21	
Pharyngitis	Additional description: Pharyngitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	19 / 233 (8.15%)	21 / 233 (9.01%)	
occurrences (all)	27	37	
Sinusitis	Additional description: Sinusitis		
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 233 (7.30%)	38 / 233 (16.31%)	
occurrences (all)	21	83	
Rhinitis	Additional description: Rhinitis		
alternative assessment type: Non-			

systematic			
subjects affected / exposed	35 / 233 (15.02%)	38 / 233 (16.31%)	
occurrences (all)	65	71	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
alternative assessment type: Non-systematic			
subjects affected / exposed	42 / 233 (18.03%)	33 / 233 (14.16%)	
occurrences (all)	47	48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2007	<p>Change to SAE reporting:</p> <ul style="list-style-type: none">- Deaths due to disease progression are no longer excluded from being reported as an SAE. <p>Governance and funding changes in protocol:</p> <ul style="list-style-type: none">- Administrative changes throughout the protocol.- Clarification of funding arrangements. <p>Addition of new sites.</p> <ul style="list-style-type: none">- Change of PI.
17 August 2007	<p>Pre-treatment evaluation (protocol): This should be completed within 4 weeks of randomisation. Cholesterol (no longer fasting) levels taken any time within 3-6 months of randomisation. C-reactive protein levels being measured.</p> <p>Change to exclusion criteria point 16 (protocol): Patients treated with insulin will be excluded.</p> <p>point 3 (protocol): >=T2 TCC or previous history of >=T2.</p> <p>Change to inclusion criteria Point 4 (protocol): No evidence of upper tract TCC on imaging studies within the past 36 months or before randomisation.</p> <p>Addition of new sites.</p> <p>Change of Principal Investigator.</p> <p>Extension of Quality of Life sub study follow-up period. This will now be for 2 years (24 months)</p>

08 May 2008	<p>Amendment of the exclusion criteria (protocol) point 12 (protocol): Chronic use of NSAIDs is defined as a frequency of 1 or more a day for more than 50 consecutive days in a year.</p> <p>Addition of new sites.</p> <p>Change of Principal Investigator.</p> <p>Extension of Quality of Life sub study follow-up period. This will now be for 3 years (36 months).</p> <p>Amendment to sample collection sub-study PIS The organisers of this study would also consider requests to use these samples for other high quality research studies. The text following this (which was already present in the previous approved version (version 3 25/10/06) confirms that the patient's confidentiality will be protected and that these other research studies would need to have ethics approval to use these samples.</p> <p>Amendment to biological sample collection consent form Am aware that my samples may be used for other research studies. The text following this sentence confirms again this states that the patient's confidentiality will be protected and that these other research studies would need to have ethics approval to use these samples.</p>
19 December 2008	<p>Inclusion criteria, point 1 more pragmatic definition of tumour size: Large tumours are defined as equal to or greater than 3cm however when tumour size is not documented tumours described as "large" are considered to be equal to or greater than 3cm and is at the discretion of the urologist. Small tumours are those which are less than 3cm in size.</p> <p>Extension of timeframe between TUR and entry into BOXIT: Randomisation should occur ideally within 6 weeks however up to 10 weeks is allowed where a delay has been unavoidable.</p> <p>Addition of appendix 2 - BOXIT-T with further explanation of BOXIT-T aims and information regarding the collection and storage of BOXIT-T samples.</p> <p>Comprehensive description of the role of the cardio-vascular sub committee</p> <p>ADDITIONAL DOCUMENTATION</p> <ul style="list-style-type: none"> - Quality of Life extension letters (version 1 19/12/2008) to patients currently participating in the Quality of Life sub-study informing them that the follow-up has been extended for up to 3 years post randomisation (extension approved in Amendment 3) and that we would like them to continue to participate in this substudy if they wish. - Quality of Life baseline patient letters (BCG and no BCG Version 2 19/12/2008) explaining that the - Quality of Life sub-study will be follow-up for 3 years. - Quality of Life follow-up patient letter (version 2 19/12/2008), this has not changed in content but will now be sent to patients not receiving BCG as well as those receiving BCG due to the extension of the Quality of Life sub-study. - Amendment to patient information sheet (version 3 19/12/2008) explaining that the Quality of Life follow-up has been extended up to 3 <p>Addition of new sites. Change of Principal Investigator.</p>
18 February 2009	<p>Amendment submitted in error: The Chief Investigator Mr. John. D. Kelly has taken up a new post at University College London. Prof. David. E. Neal would therefore be the Chief Investigator for the study.</p>
05 March 2009	<p>Correction following substantial amendment number 5 which was submitted in error, stating a change of Chief Investigator. Professor John Kelly remains the Chief Investigator for BOXIT. Professor David Neal is not the Chief Investigator for BOXIT he is the Principal Investigator at Addenbrooke's Hospital.</p>

10 June 2009	<p>INCLUSION CRITERIA (page 10, protocol V1.6)</p> <p>Pt.1. The description of the eligible risk groups (intermediate and high risk patient groups) have been simplified and the full definitions have been placed in appendix 4. The terminology used in these definitions has been amended for the number of bladder tumours/occurrences in the past year for clarification following centre feedback. The number of high and intermediate risk patients to be randomised has also been inserted.</p> <p>Pt. 2. Patients who are equal to or greater (inserted)than 18 years of age would be eligible to enter BOXIT.</p> <p>EXCLUSION CRITERIA (page 11, protocol V1.6)</p> <p>Pt. 4. The definition of a significant bleeding disorder has been further described for clarification.</p> <p>Pt. 14.The use of corticosteroids has been amended to specify that only patient use of oral corticosteroids would be excluded.</p> <p>Pt. 15. The stages of the degree of heart failure has been clarified and full definitions of these stages have been inserted into the appendices (appendix 10). Clarification of patient entry criteria for those patients who are hypertensive. Inserted additional exclusion, patients with documented abdominal aortic aneurysm.</p> <p>Pt. 18. The time frame since other malignancy and patient entry has been reduced from 5 years to 2 years.</p> <p>Patients with prostate cancer who have a life expectancy of over 5 years upon trial entry would also now be eligible to enter BOXIT.</p> <p>Reference to superficial TCC of the bladder has been changed to non-muscle invasive TCC of the bladder, to bring in line with current terminology. In addition minor changes have been made throughout the protocol for clarification purposes, please see comments in track changes version of protocol.</p> <p>Addition of new sites and change of principal investigators at existing sites.</p>
10 June 2009	Addition of new sites and change of principal investigators at existing sites.
24 November 2009	Temporary suspension of recruitment pending replacement o expiring study drug stocks.
24 November 2009	Randomisation of new patients has been re-opened after the resupply of expiring drug stock at participating centres has been completed.
23 June 2010	Reduction in sample size.
21 September 2010	Transfer of all samples collected for the BOXIT-T sub study from Cambridge University Hospitals NHS Trust to University College Hospital NHS Foundation Trust.
27 January 2011	<p>The previous version 3.0 of the protocol, version 5.0 of the BOXIT-T PIS and consent form and version 1 of the patient letter specified a specific biobank for storage of the BOXIT-T samples. The location of sample storage has since changed but is still within UCL NHS Foundation Trust. Therefore the storage location has been relaxed to read 'central UCL Biorepository'.</p> <p>In addition, there is a need for the Patient Information Sheet to be provided in a larger font size for the patient population in the BOXIT Study. The font size of the Sample Collection Sub-Study patient information sheet has been increased. There has been no change to the content of the PIS, but in increasing the font size, the number of pages have increased from 3 to 4. This is not a version change. This large font PIS will run in parallel to version 5.1 of the Sample Collection Sub- Study PIS and the version 5.1 consent form will still apply.</p>
06 June 2011	Change in trial sponsor of the BOXIT Trial
14 July 2011	Approval of the patient card issued to patients
10 October 2011	Increase to the sample size

10 February 2012	Change to the ECG reporting requirements during follow-up
31 May 2012	Change to the specified BCG strain for standard treatment.
07 January 2013	The BOXIT trial management group reviewed the requirements for long-term follow-up for the trial at their recent meeting in November 2012. It was agreed that the protocol should be clarified to confirm that annual long term follow-up should be collected from year 5 onwards for all patients. The first time-point for long term follow-up to be conducted is year 6 (72 months) after the date of randomisation, and annually thereafter.
06 January 2014	Introduction of a new Patient Information Sheet (PIS) providing information relating to the request for patients to stop taking study their study medication.
08 June 2017	Amendment to long-term follow-up of patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30279015>

<http://www.ncbi.nlm.nih.gov/pubmed/32144049>

<http://www.ncbi.nlm.nih.gov/pubmed/24612661>