# 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 |

### 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 |

| | |
|---|---|
| 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 | Investigator, Monitor, Subject, 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 |

Arm description:

Patients were randomised to placebo twice daily for 2 yr.

| | |
|---|---|
| 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:

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 |
| 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. | |
| Subject analysis set title | Celecoxib - Per protocol population |
| Subject analysis set type | Per protocol |
| 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 |
| Subject analysis set type | Per protocol |
| 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 |
| 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 |
| 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**

No statistical analyses for this end point

## 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) |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 14.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo |
| Reporting group description: - | |
| Reporting group title | Celecoxib |

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 | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |
| Pneumonia | Additional description: 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 | | | |

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

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|---|---|---|---|
| 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- | | | |

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|---|---|---|---|
| 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 | Change to SAE reporting:<br>- Deaths due to disease progression are no longer excluded from being reported as an SAE.<br><br>Governance and funding changes in protocol:<br>- Administrative changes throughout the protocol.<br>- Clarification of funding arrangements.<br><br>Addition of new sites.<br>- Change of PI. |
| 17 August 2007 | Pre-treatment evaluation (protocol):<br>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.<br><br>Change to exclusion criteria<br>point 16 (protocol):<br>Patients treated with insulin will be excluded.<br>point 3 (protocol):<br>>=T2 TCC or previous history of >=T2.<br><br>Change to inclusion criteria<br>Point 4 (protocol):<br>No evidence of upper tract TCC on imaging studies within the past 36 months or before randomisation.<br><br>Addition of new sites.<br><br>Change of Principal Investigator.<br><br>Extension of Quality of Life sub study follow-up period. This will now be for 2 years (24 months |

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| 08 May 2008 | 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.<br><br>Addition of new sites.<br><br>Change of Principal Investigator.<br><br>Extension of Quality of Life sub study follow-up period. This will now be for 3 years (36 months).<br><br>Amendment to sample collection sub-study PIS<br>The organisers of this study would also consider requests to use these samples for other high quality research studies.<br>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.<br><br>Amendment to biological sample collection consent form<br>Am aware that my samples may be used for other research studies.<br>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. |
| 19 December 2008 | Inclusion criteria, point 1 more pragmatic definition of tumour size:<br>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 that 3cm and is at the discretion of the urologist. Small tumours are those which are less than 3cm in size.<br><br>Extension of timeframe between TUR and entry into BOXIT:<br>Randomisation should occur ideally within 6 weeks however up to 10 weeks is allowed where a delay has been unavoidable.<br><br>Addition of appendix 2 - BOXIT-T with further explanation of BOXIT-T aims and information regarding the collection and storage of BOXIT-T samples.<br><br>Comprehensive description of the role of the cardio-vascular sub committee<br><br>ADDITIONAL DOCUMENTATION<br>- 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.<br>- Quality of Life baseline patient letters (BCG and no BCG Version 2 19/12/2008) explaining that the<br>- Quality of Life sub-study will be follow-up for 3 years.<br>- 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.<br>- Amendment to patient information sheet (version 3 19/12/2008) explaining that the Quality of Life follow-up has been extended up to 3<br><br>Addition of new sites.<br>Change of Principal Investigator. |
| 18 February 2009 | 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. |
| 05 March 2009 | Correction following substantial amendment number 5 which was submitted in error, stating a change of Chief Investigator.<br>Professor John Kelly remains the Chief Investigator for BOXIT.<br>Professor David Neal is not the Chief Investigator for BOXIT he is the Principal Investigator at Addenbrooke's Hospital. |

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| 10 June 2009 | INCLUSION CRITERIA (page 10, protocol V1.6)<br>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.<br>Pt. 2. Patients who are equal to or greater (inserted)than 18 years of age would be eligible to enter BOXIT.<br>EXCLUSION CRITERIA (page 11, protocol V1.6)<br>Pt. 4. The definition of a significant bleeding disorder has been further described for clarification.<br>Pt. 14.The use of corticosteroids has been amended to specifiy that only patient use of oral corticosteroids<br>would be excluded.<br>Pt. 15. The stages of the degree of heart failure has been clarified and full defintions of these stages have<br>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.<br>Pt. 18. The time frame since other malignancy and patient entry has been reduced from 5 years to 2 years.<br>Patients with prostate cancer who have a life expectancy of over 5 years upon trial entry would also now be eligible to enter BOXIT.<br>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.<br>Addition of new sites and change of principal investigators at existing sites. |
| 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 | 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'.<br><br>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<br>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<br>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. |
| 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 |

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|---|---|
| 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.

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| 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