



## Clinical trial results: Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy Summary

EudraCT number	2004-000193-31
Trial protocol	GB
Global end of trial date	

### Results information

Result version number	v1
This version publication date	27 February 2021
First version publication date	27 February 2021

### Trial information

#### Trial identification

Sponsor protocol code	PR08
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#### Additional study identifiers

ISRCTN number	ISRCTN78818544
ClinicalTrials.gov id (NCT number)	NCT00268476
WHO universal trial number (UTN)	-
Other trial identifiers	CTA: 20363/0404/001, MREC: 04/MRE07/35, Previous IRAS (Minimal Data Set): 31586

Notes:

### Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E6BT
Public contact	STAMPEDE Trial Team, MRCCTU at UCL, adrian.cook@ucl.ac.uk
Scientific contact	STAMPEDE Trial Team, MRCCTU at UCL, 44 76704700, adrian.cook@ucl.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	Interim
Date of interim/final analysis	13 May 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 May 2015
Global end of trial reached?	No

Notes:

## General information about the trial

Main objective of the trial:

This study aims to look at how to improve the way in which prostate cancer is currently managed i.e. by adding new treatments to the standard of care, whether it can enable men to live longer or, by modifying the type of hormone therapy, live at least as long and enjoy a better quality of life. The principal research question for most arms is whether the treatment concerned improves overall survival; however some comparisons such as metformin are being looked at for other reasons.

Protection of trial subjects:

In routine care

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2004
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: 11643
Country: Number of subjects enrolled	Switzerland: 95
Worldwide total number of subjects	11738
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)	4030
From 65 to 84 years	7683
85 years and over	25

## Subject disposition

### Recruitment

Recruitment details:

First patient randomised 17Oct2005

### Pre-assignment

Screening details:

Screening data not available centrally

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Arm A (SOC for B,C,E comparisons)

Arm description:

Reference patients for A vs B, C , E

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Arm B

Arm description:

Zoledronic acid

Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intravenous use

Dosage and administration details:

4mg at six 3-weekly cycles, then 4-weekly until 2 years

<b>Arm title</b>	Arm C
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Arm description:

Docetaxel

Arm type	Experimental
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

75mg/m2 for six 3-weekly cycles

<b>Arm title</b>	Arm E
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Arm description:

Zoledronic Acid and Docetaxel

Arm type	Experimental
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Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intravenous use
Dosage and administration details: 4mg at six 3-weekly cycles, then 4-weekly until 2 years	
Investigational medicinal product name	Docetaxel
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intravenous use
Dosage and administration details: 75mg/m2 for six 3-weekly cycles	
<b>Arm title</b>	Arm A (SOC for D,F comparisons)
Arm description: Reference patients for A vs D, F	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Arm D
Arm description: Celecoxib	
Arm type	Experimental
Investigational medicinal product name	Celecoxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 400mg twice a day for 1 year	
<b>Arm title</b>	Arm F
Arm description: Zoledronic Acid and Celecoxib	
Arm type	Experimental
Investigational medicinal product name	Zoledronic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in administration system
Routes of administration	Intravenous use
Dosage and administration details: 4mg at six 3-weekly cycles, then 4-weekly until 2 years	
Investigational medicinal product name	Celecoxib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 400mg twice a day for 1 year	

Number of subjects in period 1 <sup>[1]</sup>	Arm A (SOC for B,C,E comparisons)	Arm B	Arm C
Started	1184	593	592
Completed	1184	593	592

Number of subjects in period 1 <sup>[1]</sup>	Arm E	Arm A (SOC for D,F comparisons)	Arm D
Started	593	622	312
Completed	593	622	312

Number of subjects in period 1 <sup>[1]</sup>	Arm F
Started	311
Completed	311

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Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Trial arms are reported as each arm closes. Control patients (Arm A) are contemporaneously matched to experimental arms.

## Baseline characteristics

Reporting groups	
Reporting group title	Arm A (SOC for B,C,E comparisons)
Reporting group description:	
Reference patients for A vs B, C , E	
Reporting group title	Arm B
Reporting group description:	
Zoledronic acid	
Reporting group title	Arm C
Reporting group description:	
Docetaxel	
Reporting group title	Arm E
Reporting group description:	
Zoledronic Acid and Docetaxel	
Reporting group title	Arm A (SOC for D,F comparisons)
Reporting group description:	
Reference patients for A vs D, F	
Reporting group title	Arm D
Reporting group description:	
Celecoxib	
Reporting group title	Arm F
Reporting group description:	
Zoledronic Acid and Celecoxib	

Reporting group values	Arm A (SOC for B,C,E comparisons)	Arm B	Arm C
Number of subjects	1184	593	592
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	521	265	270
From 65-84 years	663	328	322
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	0	0	0
Male	1184	593	592

Reporting group values	Arm E	Arm A (SOC for D,F comparisons)	Arm D
Number of subjects	593	622	312

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	252	294	139
From 65-84 years	341	328	173
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	593	622	312

Reporting group values	Arm F	Total	
Number of subjects	311	4207	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	146	1887	
From 65-84 years	164	2319	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	0	0	
Male	311	4207	

### Subject analysis sets

Subject analysis set title	Arm A (SOC for B,C,E comparisons)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Reference patients (ABCE comparison)	
Subject analysis set title	Arm B (ZA)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Experimental group, AB comparison	
Subject analysis set title	Arm C (doce)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Arm A vs C	
Subject analysis set title	Arm E (doce+ZA)

Subject analysis set type	Intention-to-treat
Subject analysis set description: Docetaxel and Zoledronic acid	
Subject analysis set title	Arm A (SOC for D,F comparisons)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Reference patients (ADF comparisons)	
Subject analysis set title	Arm D (cel)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Arm A vs D	
Subject analysis set title	Arm F (cel+ZA)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Arm A vs F	

Reporting group values	Arm A (SOC for B,C,E comparisons)	Arm B (ZA)	Arm C (doce)
Number of subjects	1184	593	592
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	521	265	270
From 65-84 years	663	328	322
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	0	0	0
Male	1184	593	592

Reporting group values	Arm E (doce+ZA)	Arm A (SOC for D,F comparisons)	Arm D (cel)
Number of subjects	593	622	312
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	252	294	139
From 65-84 years	341	328	173
85 years and over	0	0	0



Gender categorical Units: Subjects			
Female	0	0	0
Male	593	622	312

<b>Reporting group values</b>	Arm F (cel+ZA)		
Number of subjects	311		
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)	146		
From 65-84 years	164		
85 years and over	1		
Gender categorical Units: Subjects			
Female	0		
Male	311		

## End points

### End points reporting groups

Reporting group title	Arm A (SOC for B,C,E comparisons)
Reporting group description: Reference patients for A vs B, C , E	
Reporting group title	Arm B
Reporting group description: Zoledronic acid	
Reporting group title	Arm C
Reporting group description: Docetaxel	
Reporting group title	Arm E
Reporting group description: Zoledronic Acid and Docetaxel	
Reporting group title	Arm A (SOC for D,F comparisons)
Reporting group description: Reference patients for A vs D, F	
Reporting group title	Arm D
Reporting group description: Celecoxib	
Reporting group title	Arm F
Reporting group description: Zoledronic Acid and Celecoxib	
Subject analysis set title	Arm A (SOC for B,C,E comparisons)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Reference patients (ABCE comparison)	
Subject analysis set title	Arm B (ZA)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Experimental group, AB comparison	
Subject analysis set title	Arm C (doce)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Arm A vs C	
Subject analysis set title	Arm E (doce+ZA)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Docetaxel and Zoledronic acid	
Subject analysis set title	Arm A (SOC for D,F comparisons)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Reference patients (ADF comparisons)	
Subject analysis set title	Arm D (cel)
Subject analysis set type	Intention-to-treat
Subject analysis set description: Arm A vs D	
Subject analysis set title	Arm F (cel+ZA)
Subject analysis set type	Intention-to-treat

**Primary: Overall survival**

End point title	Overall survival
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End point description:
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End point type	Primary
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End point timeframe:
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Event driven analysis
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End point values	Arm A (SOC for B,C,E comparisons)	Arm B (ZA)	Arm C (doce)	Arm E (doce+ZA)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1184	593	592	593
Units: Patients				
Died	415	201	175	187

End point values	Arm A (SOC for D,F comparisons)	Arm D (cel)	Arm F (cel+ZA)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	622	312	311	
Units: Patients				
Died	303	143	138	

**Statistical analyses**

<b>Statistical analysis title</b>	Zoledronic Acid vs SOC
Comparison groups	Arm A (SOC for B,C,E comparisons) v Arm B (ZA)
Number of subjects included in analysis	1777
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.45
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.11

<b>Statistical analysis title</b>	Docetaxel vs SOC
Comparison groups	Arm A (SOC for B,C,E comparisons) v Arm C (doce)
Number of subjects included in analysis	1776
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.93

<b>Statistical analysis title</b>	Docetaxel+Zoledronic Acid vs SOC
Comparison groups	Arm A (SOC for B,C,E comparisons) v Arm E (doce+ZA)
Number of subjects included in analysis	1777
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.022
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	0.97

<b>Statistical analysis title</b>	Celecoxib vs SOC
Comparison groups	Arm D (cel) v Arm A (SOC for D,F comparisons)
Number of subjects included in analysis	934
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.847
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.2

<b>Statistical analysis title</b>	Celecoxib + Zoledronic acid vs SOC
Comparison groups	Arm A (SOC for D,F comparisons) v Arm F (cel+ZA)
Number of subjects included in analysis	933
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.05

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Events to March 4 2015 for A vs B,C,E comparisons

Events to December 15 2015 for A vs D,F comparisons

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
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Dictionary version	4.0
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### Reporting groups

Reporting group title	SOC (Arm A, ABCE comparison)
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Reporting group description:

Reference patients, Arm A, randomised between A,B,C,E

Reporting group title	ZA (Arm B)
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Reporting group description:

Experimental patients, AB comparison

Reporting group title	Doce (Arm C)
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Reporting group description:

Arm C docetaxel patients

Reporting group title	Doce+ZA (Arm E)
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Reporting group description:

Docetaxel plus Zoledronic acid

Reporting group title	SOC (Arm A, ADF comparison)
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Reporting group description:

Reference patients, Arm A, randomised between A,D,F

Reporting group title	Celecoxib (Arm D)
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Reporting group description:

Experimental arm, celecoxib comparison

Reporting group title	Celecoxib + ZA
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Reporting group description:

(Arm F)

Serious adverse events	SOC (Arm A, ABCE comparison)	ZA (Arm B)	Doce (Arm C)
Total subjects affected by serious adverse events			
subjects affected / exposed	59 / 1184 (4.98%)	30 / 593 (5.06%)	126 / 592 (21.28%)
number of deaths (all causes)	415	201	175
number of deaths resulting from adverse events	0	0	1
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	7 / 1184 (0.59%)	4 / 593 (0.67%)	5 / 592 (0.84%)
occurrences causally related to treatment / all	0 / 7	0 / 4	1 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Arrhythmia			

subjects affected / exposed	2 / 1184 (0.17%)	1 / 593 (0.17%)	2 / 592 (0.34%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 1184 (0.00%)	2 / 593 (0.34%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 1184 (0.42%)	3 / 593 (0.51%)	2 / 592 (0.34%)
occurrences causally related to treatment / all	0 / 8	0 / 3	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	7 / 1184 (0.59%)	3 / 593 (0.51%)	77 / 592 (13.01%)
occurrences causally related to treatment / all	0 / 7	0 / 4	79 / 83
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 1184 (0.08%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	1 / 1184 (0.08%)	0 / 593 (0.00%)	3 / 592 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 1184 (0.17%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Oedema			
subjects affected / exposed	1 / 1184 (0.08%)	0 / 593 (0.00%)	4 / 592 (0.68%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	3 / 1184 (0.25%)	2 / 593 (0.34%)	6 / 592 (1.01%)
occurrences causally related to treatment / all	0 / 3	0 / 2	5 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 1184 (0.00%)	1 / 593 (0.17%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 1184 (0.17%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	2 / 1184 (0.17%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1184 (0.08%)	0 / 593 (0.00%)	8 / 592 (1.35%)
occurrences causally related to treatment / all	0 / 1	0 / 0	8 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 1184 (0.34%)	4 / 593 (0.67%)	2 / 592 (0.34%)
occurrences causally related to treatment / all	0 / 4	0 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	3 / 1184 (0.25%)	1 / 593 (0.17%)	3 / 592 (0.51%)
occurrences causally related to treatment / all	0 / 3	0 / 1	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0



Diarrhoea			
subjects affected / exposed	5 / 1184 (0.42%)	1 / 593 (0.17%)	8 / 592 (1.35%)
occurrences causally related to treatment / all	0 / 5	0 / 1	5 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	2 / 592 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 1184 (0.17%)	2 / 593 (0.34%)	3 / 592 (0.51%)
occurrences causally related to treatment / all	0 / 2	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	2 / 1184 (0.17%)	1 / 593 (0.17%)	2 / 592 (0.34%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	1 / 1184 (0.08%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	2 / 592 (0.34%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	4 / 1184 (0.34%)	3 / 593 (0.51%)	5 / 592 (0.84%)
occurrences causally related to treatment / all	0 / 4	0 / 3	4 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Nail discolouration			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 1184 (0.00%)	1 / 593 (0.17%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	5 / 1184 (0.42%)	2 / 593 (0.34%)	6 / 592 (1.01%)
occurrences causally related to treatment / all	0 / 6	0 / 2	2 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	4 / 1184 (0.34%)	2 / 593 (0.34%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	2 / 1184 (0.17%)	2 / 593 (0.34%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	4 / 1184 (0.34%)	3 / 593 (0.51%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Insomnia			

subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	3 / 1184 (0.25%)	2 / 593 (0.34%)	3 / 592 (0.51%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 1184 (0.08%)	1 / 593 (0.17%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Glucose tolerance decreased			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 1184 (0.08%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorexia nervosa			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	1 / 1184 (0.08%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypophosphataemia			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	1 / 592 (0.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Doce+ZA (Arm E)	SOC (Arm A, ADF comparison)	Celecoxib (Arm D)
Total subjects affected by serious adverse events			
subjects affected / exposed	134 / 593 (22.60%)	35 / 622 (5.63%)	15 / 312 (4.81%)
number of deaths (all causes)	187	303	143
number of deaths resulting from adverse events	2	0	0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	5 / 593 (0.84%)	5 / 622 (0.80%)	2 / 312 (0.64%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Arrhythmia			
subjects affected / exposed	6 / 593 (1.01%)	0 / 622 (0.00%)	2 / 312 (0.64%)
occurrences causally related to treatment / all	2 / 7	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart failure			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 593 (0.34%)	1 / 622 (0.16%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	65 / 593 (10.96%)	4 / 622 (0.64%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	66 / 73	0 / 4	0 / 0
deaths causally related to treatment / all	2 / 2	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	9 / 593 (1.52%)	1 / 622 (0.16%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	9 / 9	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 593 (0.34%)	1 / 622 (0.16%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fever			
subjects affected / exposed	17 / 593 (2.87%)	2 / 622 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	5 / 18	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 593 (0.17%)	1 / 622 (0.16%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	2 / 593 (0.34%)	2 / 622 (0.32%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	4 / 593 (0.67%)	1 / 622 (0.16%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	7 / 593 (1.18%)	3 / 622 (0.48%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 7	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 593 (0.17%)	3 / 622 (0.48%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	10 / 593 (1.69%)	4 / 622 (0.64%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	5 / 11	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	6 / 593 (1.01%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	3 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	6 / 593 (1.01%)	2 / 622 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	2 / 7	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 593 (0.17%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			

subjects affected / exposed	5 / 593 (0.84%)	0 / 622 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	1 / 593 (0.17%)	1 / 622 (0.16%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	1 / 593 (0.17%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	5 / 593 (0.84%)	2 / 622 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	2 / 5	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Nail discolouration			
subjects affected / exposed	1 / 593 (0.17%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	2 / 593 (0.34%)	0 / 622 (0.00%)	2 / 312 (0.64%)
occurrences causally related to treatment / all	1 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	4 / 593 (0.67%)	2 / 622 (0.32%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 593 (0.34%)	2 / 622 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Haematuria			
subjects affected / exposed	3 / 593 (0.51%)	2 / 622 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	3 / 593 (0.51%)	2 / 622 (0.32%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 593 (0.17%)	3 / 622 (0.48%)	1 / 312 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 593 (0.17%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Glucose tolerance decreased			



subjects affected / exposed	1 / 593 (0.17%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anorexia nervosa			
subjects affected / exposed	1 / 593 (0.17%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypophosphataemia			
subjects affected / exposed	0 / 593 (0.00%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	Celecoxib + ZA		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 311 (10.61%)		
number of deaths (all causes)	138		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Arrhythmia			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Heart failure			

subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 311 (0.96%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Fever			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 311 (1.93%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	3 / 311 (0.96%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Nausea			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Upper respiratory tract infection			
subjects affected / exposed	3 / 311 (0.96%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	3 / 311 (0.96%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Nail discolouration			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Rash			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	2 / 311 (0.64%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cognitive disorder			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Glucose tolerance decreased			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	1 / 311 (0.32%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Anorexia nervosa			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypophosphataemia			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	SOC (Arm A, ABCE comparison)	ZA (Arm B)	Doce (Arm C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1152 / 1184 (97.30%)	579 / 593 (97.64%)	571 / 592 (96.45%)
Vascular disorders			
Hypertension			
subjects affected / exposed	84 / 1184 (7.09%)	50 / 593 (8.43%)	44 / 592 (7.43%)
occurrences (all)	129	90	74
Hot flush			
subjects affected / exposed	968 / 1184 (81.76%)	462 / 593 (77.91%)	454 / 592 (76.69%)
occurrences (all)	5324	2400	2425
General disorders and administration site conditions			
Fever			
subjects affected / exposed	29 / 1184 (2.45%)	38 / 593 (6.41%)	49 / 592 (8.28%)
occurrences (all)	39	51	58
Fatigue			
subjects affected / exposed	632 / 1184 (53.38%)	342 / 593 (57.67%)	431 / 592 (72.80%)
occurrences (all)	1999	1144	1616
Oedema			
subjects affected / exposed	151 / 1184 (12.75%)	68 / 593 (11.47%)	147 / 592 (24.83%)
occurrences (all)	320	112	324
Influenza like illness			
subjects affected / exposed	97 / 1184 (8.19%)	215 / 593 (36.26%)	87 / 592 (14.70%)
occurrences (all)	125	363	119
Pain			
subjects affected / exposed	363 / 1184 (30.66%)	240 / 593 (40.47%)	189 / 592 (31.93%)
occurrences (all)	720	485	385
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	39 / 1184 (3.29%)	21 / 593 (3.54%)	58 / 592 (9.80%)
occurrences (all)	47	24	69
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	586 / 1184 (49.49%)	296 / 593 (49.92%)	277 / 592 (46.79%)
occurrences (all)	3230	1587	1545
Gynaecomastia			

subjects affected / exposed occurrences (all)	84 / 1184 (7.09%) 145	38 / 593 (6.41%) 57	29 / 592 (4.90%) 41
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	129 / 1184 (10.90%) 229	56 / 593 (9.44%) 73	95 / 592 (16.05%) 152
Dyspnoea subjects affected / exposed occurrences (all)	171 / 1184 (14.44%) 362	82 / 593 (13.83%) 154	122 / 592 (20.61%) 256
Rhinitis subjects affected / exposed occurrences (all)	62 / 1184 (5.24%) 102	32 / 593 (5.40%) 55	41 / 592 (6.93%) 71
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	291 / 1184 (24.58%) 784	152 / 593 (25.63%) 362	189 / 592 (31.93%) 457
Investigations Neutrophil count subjects affected / exposed occurrences (all)  Alanine aminotransferase subjects affected / exposed occurrences (all)	46 / 1184 (3.89%) 82  110 / 1184 (9.29%) 218	25 / 593 (4.22%) 37  55 / 593 (9.27%) 102	115 / 592 (19.43%) 161  69 / 592 (11.66%) 139
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	141 / 1184 (11.91%) 252	75 / 593 (12.65%) 152	88 / 592 (14.86%) 141
Headache subjects affected / exposed occurrences (all)	161 / 1184 (13.60%) 334	86 / 593 (14.50%) 153	95 / 592 (16.05%) 190
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	322 / 1184 (27.20%) 931	212 / 593 (35.75%) 653	228 / 592 (38.51%) 691
Eye disorders			



Vision blurred subjects affected / exposed occurrences (all)	54 / 1184 (4.56%) 85	27 / 593 (4.55%) 54	44 / 592 (7.43%) 73
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	160 / 1184 (13.51%) 298	76 / 593 (12.82%) 131	114 / 592 (19.26%) 200
Constipation subjects affected / exposed occurrences (all)	218 / 1184 (18.41%) 440	147 / 593 (24.79%) 278	207 / 592 (34.97%) 389
Diarrhoea subjects affected / exposed occurrences (all)	251 / 1184 (21.20%) 495	139 / 593 (23.44%) 250	247 / 592 (41.72%) 499
Dyspepsia subjects affected / exposed occurrences (all)	155 / 1184 (13.09%) 314	76 / 593 (12.82%) 123	137 / 592 (23.14%) 245
Flatulence subjects affected / exposed occurrences (all)	167 / 1184 (14.10%) 395	79 / 593 (13.32%) 160	88 / 592 (14.86%) 158
Haemorrhage subjects affected / exposed occurrences (all)	90 / 1184 (7.60%) 148	36 / 593 (6.07%) 70	44 / 592 (7.43%) 71
Nausea subjects affected / exposed occurrences (all)	128 / 1184 (10.81%) 210	77 / 593 (12.98%) 131	151 / 592 (25.51%) 226
Vomiting subjects affected / exposed occurrences (all)	61 / 1184 (5.15%) 81	30 / 593 (5.06%) 39	57 / 592 (9.63%) 73
Stomatitis subjects affected / exposed occurrences (all)	36 / 1184 (3.04%) 57	25 / 593 (4.22%) 31	153 / 592 (25.84%) 210
Hepatobiliary disorders			
Hepatic failure subjects affected / exposed occurrences (all)	65 / 1184 (5.49%) 105	35 / 593 (5.90%) 69	37 / 592 (6.25%) 71

Skin and subcutaneous tissue disorders			
Nail discolouration			
subjects affected / exposed	61 / 1184 (5.15%)	37 / 593 (6.24%)	258 / 592 (43.58%)
occurrences (all)	109	51	583
Rash			
subjects affected / exposed	117 / 1184 (9.88%)	67 / 593 (11.30%)	73 / 592 (12.33%)
occurrences (all)	199	91	104
Alopecia			
subjects affected / exposed	7 / 1184 (0.59%)	2 / 593 (0.34%)	80 / 592 (13.51%)
occurrences (all)	7	3	136
Renal and urinary disorders			
Urine output			
subjects affected / exposed	605 / 1184 (51.10%)	308 / 593 (51.94%)	307 / 592 (51.86%)
occurrences (all)	2125	957	969
Acute kidney injury			
subjects affected / exposed	92 / 1184 (7.77%)	71 / 593 (11.97%)	49 / 592 (8.28%)
occurrences (all)	183	232	95
Haematuria			
subjects affected / exposed	0 / 1184 (0.00%)	0 / 593 (0.00%)	0 / 592 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	144 / 1184 (12.16%)	69 / 593 (11.64%)	64 / 592 (10.81%)
occurrences (all)	246	109	107
Myalgia			
subjects affected / exposed	184 / 1184 (15.54%)	109 / 593 (18.38%)	133 / 592 (22.47%)
occurrences (all)	316	186	226
Arthralgia			
subjects affected / exposed	303 / 1184 (25.59%)	189 / 593 (31.87%)	202 / 592 (34.12%)
occurrences (all)	787	426	513
Bone pain			
subjects affected / exposed	436 / 1184 (36.82%)	235 / 593 (39.63%)	191 / 592 (32.26%)
occurrences (all)	920	531	442
Infections and infestations			

Urinary tract infection subjects affected / exposed occurrences (all)	94 / 1184 (7.94%) 119	57 / 593 (9.61%) 73	81 / 592 (13.68%) 108
Metabolism and nutrition disorders Hypocalcaemia subjects affected / exposed occurrences (all)	39 / 1184 (3.29%) 55	64 / 593 (10.79%) 98	32 / 592 (5.41%) 42
Anorexia nervosa subjects affected / exposed occurrences (all)	91 / 1184 (7.69%) 120	49 / 593 (8.26%) 78	73 / 592 (12.33%) 85

<b>Non-serious adverse events</b>	Doce+ZA (Arm E)	SOC (Arm A, ADF comparison)	Celecoxib (Arm D)
Total subjects affected by non-serious adverse events subjects affected / exposed	560 / 593 (94.44%)	605 / 622 (97.27%)	292 / 312 (93.59%)
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	30 / 593 (5.06%) 42	35 / 622 (5.63%) 47	39 / 312 (12.50%) 63
Hot flush subjects affected / exposed occurrences (all)	442 / 593 (74.54%) 2356	495 / 622 (79.58%) 2877	229 / 312 (73.40%) 1321
General disorders and administration site conditions Fever subjects affected / exposed occurrences (all)	70 / 593 (11.80%) 84	0 / 622 (0.00%) 0	0 / 312 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	427 / 593 (72.01%) 1607	333 / 622 (53.54%) 1080	151 / 312 (48.40%) 424
Oedema subjects affected / exposed occurrences (all)	137 / 593 (23.10%) 261	88 / 622 (14.15%) 191	47 / 312 (15.06%) 81
Influenza like illness subjects affected / exposed occurrences (all)	140 / 593 (23.61%) 210	63 / 622 (10.13%) 84	27 / 312 (8.65%) 36
Pain			

subjects affected / exposed occurrences (all)	234 / 593 (39.46%) 501	187 / 622 (30.06%) 364	90 / 312 (28.85%) 162
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	42 / 593 (7.08%) 53	0 / 622 (0.00%) 0	0 / 312 (0.00%) 0
Reproductive system and breast disorders Erectile dysfunction subjects affected / exposed occurrences (all)  Gynaecomastia subjects affected / exposed occurrences (all)	281 / 593 (47.39%) 1628  37 / 593 (6.24%) 58	308 / 622 (49.52%) 1851  47 / 622 (7.56%) 74	127 / 312 (40.71%) 740  19 / 312 (6.09%) 41
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Dyspnoea subjects affected / exposed occurrences (all)  Rhinitis subjects affected / exposed occurrences (all)	79 / 593 (13.32%) 136  117 / 593 (19.73%) 253  39 / 593 (6.58%) 61	59 / 622 (9.49%) 103  82 / 622 (13.18%) 169  38 / 622 (6.11%) 65	19 / 312 (6.09%) 31  45 / 312 (14.42%) 99  17 / 312 (5.45%) 24
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	170 / 593 (28.67%) 416	154 / 622 (24.76%) 389	69 / 312 (22.12%) 142
Investigations Neutrophil count subjects affected / exposed occurrences (all)  Alanine aminotransferase subjects affected / exposed occurrences (all)	111 / 593 (18.72%) 148  63 / 593 (10.62%) 140	0 / 622 (0.00%) 0  53 / 622 (8.52%) 116	0 / 312 (0.00%) 0  29 / 312 (9.29%) 73
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	93 / 593 (15.68%) 158	90 / 622 (14.47%) 169	40 / 312 (12.82%) 69
Headache subjects affected / exposed occurrences (all)	98 / 593 (16.53%) 172	100 / 622 (16.08%) 202	35 / 312 (11.22%) 63
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	252 / 593 (42.50%) 902	172 / 622 (27.65%) 495	78 / 312 (25.00%) 255
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	61 / 593 (10.29%) 105	0 / 622 (0.00%) 0	0 / 312 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	127 / 593 (21.42%) 203	89 / 622 (14.31%) 161	60 / 312 (19.23%) 95
Constipation subjects affected / exposed occurrences (all)	212 / 593 (35.75%) 436	125 / 622 (20.10%) 268	46 / 312 (14.74%) 81
Diarrhoea subjects affected / exposed occurrences (all)	233 / 593 (39.29%) 451	134 / 622 (21.54%) 274	85 / 312 (27.24%) 143
Dyspepsia subjects affected / exposed occurrences (all)	125 / 593 (21.08%) 208	97 / 622 (15.59%) 221	67 / 312 (21.47%) 110
Flatulence subjects affected / exposed occurrences (all)	78 / 593 (13.15%) 132	105 / 622 (16.88%) 252	48 / 312 (15.38%) 89
Haemorrhage subjects affected / exposed occurrences (all)	46 / 593 (7.76%) 74	48 / 622 (7.72%) 81	15 / 312 (4.81%) 28
Nausea subjects affected / exposed occurrences (all)	152 / 593 (25.63%) 265	80 / 622 (12.86%) 126	43 / 312 (13.78%) 57
Vomiting			

subjects affected / exposed	65 / 593 (10.96%)	41 / 622 (6.59%)	23 / 312 (7.37%)
occurrences (all)	88	52	25
Stomatitis			
subjects affected / exposed	149 / 593 (25.13%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences (all)	216	0	0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	44 / 593 (7.42%)	27 / 622 (4.34%)	27 / 312 (8.65%)
occurrences (all)	78	49	52
Skin and subcutaneous tissue disorders			
Nail discolouration			
subjects affected / exposed	194 / 593 (32.72%)	35 / 622 (5.63%)	16 / 312 (5.13%)
occurrences (all)	406	53	21
Rash			
subjects affected / exposed	70 / 593 (11.80%)	70 / 622 (11.25%)	48 / 312 (15.38%)
occurrences (all)	116	126	77
Alopecia			
subjects affected / exposed	69 / 593 (11.64%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences (all)	118	0	0
Renal and urinary disorders			
Urine output			
subjects affected / exposed	279 / 593 (47.05%)	310 / 622 (49.84%)	146 / 312 (46.79%)
occurrences (all)	934	1130	514
Acute kidney injury			
subjects affected / exposed	75 / 593 (12.65%)	51 / 622 (8.20%)	25 / 312 (8.01%)
occurrences (all)	201	101	47
Haematuria			
subjects affected / exposed	0 / 593 (0.00%)	40 / 622 (6.43%)	21 / 312 (6.73%)
occurrences (all)	0	60	30
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	64 / 593 (10.79%)	87 / 622 (13.99%)	28 / 312 (8.97%)
occurrences (all)	97	154	45
Myalgia			
subjects affected / exposed	141 / 593 (23.78%)	101 / 622 (16.24%)	34 / 312 (10.90%)
occurrences (all)	265	158	60

Arthralgia			
subjects affected / exposed	214 / 593 (36.09%)	182 / 622 (29.26%)	87 / 312 (27.88%)
occurrences (all)	525	495	220
Bone pain			
subjects affected / exposed	232 / 593 (39.12%)	249 / 622 (40.03%)	114 / 312 (36.54%)
occurrences (all)	517	564	240
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	83 / 593 (14.00%)	52 / 622 (8.36%)	27 / 312 (8.65%)
occurrences (all)	104	64	30
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	57 / 593 (9.61%)	26 / 622 (4.18%)	16 / 312 (5.13%)
occurrences (all)	91	42	23
Anorexia nervosa			
subjects affected / exposed	74 / 593 (12.48%)	56 / 622 (9.00%)	32 / 312 (10.26%)
occurrences (all)	118	79	40

<b>Non-serious adverse events</b>	Celecoxib + ZA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	297 / 311 (95.50%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	27 / 311 (8.68%)		
occurrences (all)	43		
Hot flush			
subjects affected / exposed	222 / 311 (71.38%)		
occurrences (all)	1268		
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	165 / 311 (53.05%)		
occurrences (all)	536		
Oedema			

subjects affected / exposed	46 / 311 (14.79%)		
occurrences (all)	76		
Influenza like illness			
subjects affected / exposed	75 / 311 (24.12%)		
occurrences (all)	137		
Pain			
subjects affected / exposed	94 / 311 (30.23%)		
occurrences (all)	180		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	135 / 311 (43.41%)		
occurrences (all)	820		
Gynaecomastia			
subjects affected / exposed	17 / 311 (5.47%)		
occurrences (all)	32		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 311 (9.32%)		
occurrences (all)	36		
Dyspnoea			
subjects affected / exposed	38 / 311 (12.22%)		
occurrences (all)	72		
Rhinitis			
subjects affected / exposed	21 / 311 (6.75%)		
occurrences (all)	39		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	79 / 311 (25.40%)		
occurrences (all)	198		
Investigations			
Neutrophil count			



subjects affected / exposed	0 / 311 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase			
subjects affected / exposed	26 / 311 (8.36%)		
occurrences (all)	52		
Nervous system disorders			
Dizziness			
subjects affected / exposed	37 / 311 (11.90%)		
occurrences (all)	65		
Headache			
subjects affected / exposed	38 / 311 (12.22%)		
occurrences (all)	80		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	108 / 311 (34.73%)		
occurrences (all)	370		
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 311 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	54 / 311 (17.36%)		
occurrences (all)	106		
Constipation			
subjects affected / exposed	70 / 311 (22.51%)		
occurrences (all)	147		
Diarrhoea			
subjects affected / exposed	77 / 311 (24.76%)		
occurrences (all)	133		
Dyspepsia			
subjects affected / exposed	57 / 311 (18.33%)		
occurrences (all)	102		
Flatulence			
subjects affected / exposed	43 / 311 (13.83%)		
occurrences (all)	105		
Haemorrhage			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Nausea</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Stomatitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>20 / 311 (6.43%)</p> <p>35</p> <p>37 / 311 (11.90%)</p> <p>59</p> <p>24 / 311 (7.72%)</p> <p>35</p> <p>0 / 311 (0.00%)</p> <p>0</p>		
<p>Hepatobiliary disorders</p> <p>Hepatic failure</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>27 / 311 (8.68%)</p> <p>44</p>		
<p>Skin and subcutaneous tissue disorders</p> <p>Nail discolouration</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alopecia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>23 / 311 (7.40%)</p> <p>47</p> <p>41 / 311 (13.18%)</p> <p>67</p> <p>0 / 311 (0.00%)</p> <p>0</p>		
<p>Renal and urinary disorders</p> <p>Urine output</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Acute kidney injury</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Haematuria</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>138 / 311 (44.37%)</p> <p>438</p> <p>57 / 311 (18.33%)</p> <p>171</p> <p>14 / 311 (4.50%)</p> <p>16</p>		
<p>Musculoskeletal and connective tissue disorders</p>			

Back pain			
subjects affected / exposed	35 / 311 (11.25%)		
occurrences (all)	71		
Myalgia			
subjects affected / exposed	53 / 311 (17.04%)		
occurrences (all)	99		
Arthralgia			
subjects affected / exposed	94 / 311 (30.23%)		
occurrences (all)	270		
Bone pain			
subjects affected / exposed	120 / 311 (38.59%)		
occurrences (all)	301		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	34 / 311 (10.93%)		
occurrences (all)	39		
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	25 / 311 (8.04%)		
occurrences (all)	34		
Anorexia nervosa			
subjects affected / exposed	35 / 311 (11.25%)		
occurrences (all)	47		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported