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

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
Arm title	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

Arm title	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

Arm title	Arm C

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

Arm title	Arm E

Arm description:

Zoledronic Acid and Docetaxel

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	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

Arm title	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

Arm title	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

Arm title	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[1]	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[1]	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[1]	Arm F
Started	311
Completed	311

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

Reporting group values	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

Subject analysis set description:
Arm A vs F

Primary: Overall survival	
End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe:	
Event driven analysis	

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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Statistical analysis title	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

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	SOC (Arm A, ABCE comparison)
Reporting group description: Reference patients, Arm A, randomised between A,B,C,E	
Reporting group title	ZA (Arm B)
Reporting group description: Experimental patients, AB comparison	
Reporting group title	Doce (Arm C)
Reporting group description: Arm C docetaxel patients	
Reporting group title	Doce+ZA (Arm E)
Reporting group description: Docetaxel plus Zoledronic acid	
Reporting group title	SOC (Arm A, ADF comparison)
Reporting group description: Reference patients, Arm A, randomised between A,D,F	
Reporting group title	Celecoxib (Arm D)
Reporting group description: Experimental arm, celecoxib comparison	
Reporting group title	Celecoxib + ZA
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

Serious adverse events	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

Serious adverse events	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 %

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

Vision blurred			
subjects affected / exposed	54 / 1184 (4.56%)	27 / 593 (4.55%)	44 / 592 (7.43%)
occurrences (all)	85	54	73
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	160 / 1184 (13.51%)	76 / 593 (12.82%)	114 / 592 (19.26%)
occurrences (all)	298	131	200
Constipation			
subjects affected / exposed	218 / 1184 (18.41%)	147 / 593 (24.79%)	207 / 592 (34.97%)
occurrences (all)	440	278	389
Diarrhoea			
subjects affected / exposed	251 / 1184 (21.20%)	139 / 593 (23.44%)	247 / 592 (41.72%)
occurrences (all)	495	250	499
Dyspepsia			
subjects affected / exposed	155 / 1184 (13.09%)	76 / 593 (12.82%)	137 / 592 (23.14%)
occurrences (all)	314	123	245
Flatulence			
subjects affected / exposed	167 / 1184 (14.10%)	79 / 593 (13.32%)	88 / 592 (14.86%)
occurrences (all)	395	160	158
Haemorrhage			
subjects affected / exposed	90 / 1184 (7.60%)	36 / 593 (6.07%)	44 / 592 (7.43%)
occurrences (all)	148	70	71
Nausea			
subjects affected / exposed	128 / 1184 (10.81%)	77 / 593 (12.98%)	151 / 592 (25.51%)
occurrences (all)	210	131	226
Vomiting			
subjects affected / exposed	61 / 1184 (5.15%)	30 / 593 (5.06%)	57 / 592 (9.63%)
occurrences (all)	81	39	73
Stomatitis			
subjects affected / exposed	36 / 1184 (3.04%)	25 / 593 (4.22%)	153 / 592 (25.84%)
occurrences (all)	57	31	210
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	65 / 1184 (5.49%)	35 / 593 (5.90%)	37 / 592 (6.25%)
occurrences (all)	105	69	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	94 / 1184 (7.94%)	57 / 593 (9.61%)	81 / 592 (13.68%)
occurrences (all)	119	73	108
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	39 / 1184 (3.29%)	64 / 593 (10.79%)	32 / 592 (5.41%)
occurrences (all)	55	98	42
Anorexia nervosa			
subjects affected / exposed	91 / 1184 (7.69%)	49 / 593 (8.26%)	73 / 592 (12.33%)
occurrences (all)	120	78	85

Non-serious adverse events	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	30 / 593 (5.06%)	35 / 622 (5.63%)	39 / 312 (12.50%)
occurrences (all)	42	47	63
Hot flush			
subjects affected / exposed	442 / 593 (74.54%)	495 / 622 (79.58%)	229 / 312 (73.40%)
occurrences (all)	2356	2877	1321
General disorders and administration site conditions			
Fever			
subjects affected / exposed	70 / 593 (11.80%)	0 / 622 (0.00%)	0 / 312 (0.00%)
occurrences (all)	84	0	0
Fatigue			
subjects affected / exposed	427 / 593 (72.01%)	333 / 622 (53.54%)	151 / 312 (48.40%)
occurrences (all)	1607	1080	424
Oedema			
subjects affected / exposed	137 / 593 (23.10%)	88 / 622 (14.15%)	47 / 312 (15.06%)
occurrences (all)	261	191	81
Influenza like illness			
subjects affected / exposed	140 / 593 (23.61%)	63 / 622 (10.13%)	27 / 312 (8.65%)
occurrences (all)	210	84	36
Pain			

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

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

Non-serious adverse events	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			

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

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported