Clinical trial results:
A double-blind, placebo-controlled, three arm randomised multi-centre Gynaecologic Cancer InterGroup trial of AZD2171, in combination with platinum-based chemotherapy and as a single agent maintenance therapy, in women with ovarian cancer relapsing more than 6 months following completion of first line platinum-based treatment.

Summary

EudraCT number	2007-001346-41
Trial protocol	GB ES
Global end of trial date	01 October 2018

Results information

Result version number	v1 (current)
This version publication date	26 December 2020
First version publication date	26 December 2020

Trial information

Trial identification

Sponsor protocol code	ICON6

Additional study identifiers

ISRCTN number	ISRCTN68510403
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical Research Council
Sponsor organisation address	58 Victoria Embankment, London, United Kingdom,
Public contact	ICON6 Trial Manager, Medical Research Council, icon6@ctu.mrc.ac.uk
Scientific contact	ICON6 Trial Manager, Medical Research Council, icon6@ctu.mrc.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 March 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to assess the safety and efficacy of AZD2171 in combination with platinum-based chemotherapy and as a single agent maintenance therapy, in women with ovarian cancer relapsing more than 6 months following completion of first line platinum based treatment.
The main outcome measure is Progression Free Survival (PFS)

Protection of trial subjects:

Not applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 December 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United Kingdom: 380
Country: Number of subjects enrolled	Canada: 87
Country: Number of subjects enrolled	Australia: 17
Worldwide total number of subjects	486
EEA total number of subjects	382

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)	274
From 65 to 84 years	210

85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	486
Number of subjects completed	456

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Lower dose, not in final analysis: 30

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Reference

Arm description:

6 cycles of platinum-based chemotherapy plus Placebo during chemotherapy

Arm type	Placebo
Investigational medicinal product name	Carboplatin/Paclitaxel + Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Capsule
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

carboplatin AUC 6b over 30-60 minutes, in combination with paclitaxel 175 mg/m2 over three hours, three weekly for six cycles.

Arm title	Concurrent

Arm description:

6 cycles of platinum-based chemotherapy plus Cediranib during chemotherapy; then an oral daily placebo tablet up to 18 months from randomisation or until progression

Arm type	Experimental
Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

20mg; 15mg were allowed if there were toxic effects.

Arm title	Maintenance

Arm description:

6 cycles of platinum-based chemotherapy plus Cediranib during chemotherapy; plus oral cediranib daily

during chemotherapy and then continued up to 18 months from randomisation or until progression.

Arm type	Experimental
Investigational medicinal product name	Cediranib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

20mg; 15mg were allowed if there were toxic effects.

Number of subjects in period 1[1]	Reference	Concurrent	Maintenance
Started	118	174	164
Completed	118	174	164

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: The thirty participants who completed 30mg of drug are not included in the final analysis.

Baseline characteristics

Reporting groups	
Reporting group title	Reference
Reporting group description:	
6 cycles of platinum-based chemotherapy plus Placebo during chemotherapy	
Reporting group title	Concurrent
Reporting group description:	
6 cycles of platinum-based chemotherapy plus Cediranib during chemotherapy; then an oral daily placebo tablet up to 18 months from randomisation or until progression	
Reporting group title	Maintenance
Reporting group description:	
6 cycles of platinum-based chemotherapy plus Cediranib during chemotherapy; plus oral cediranib daily during chemotherapy and then continued up to 18 months from randomisation or until progression.	

Reporting group values	Reference	Concurrent	Maintenance
Number of subjects	118	174	164
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	62	62	62
inter-quartile range (Q1-Q3)	53 to 67	54 to 69	54 to 68
Gender categorical Units: Subjects			
Female	118	174	164
Male	0	0	0
ECOG Status Units: Subjects			
Zero	69	109	95
One	47	64	67
Two	1	0	0
Three	0	0	1
Not available	1	1	1
Primary tumour type Units: Subjects			
Ovary	98	139	131
Fallopian	1	6	6
Peritoneal	19	29	27

Histology Units: Subjects			
Serous	87	129	116
Endometrioid	3	7	9
Clear cell	3	8	5
Mucinous	0	3	1
Mixed or other	21	26	30
Undifferentiated	3	0	2
Not available	1	1	1
Tumour grade Units: Subjects			
Well differentiated	1	6	5
Moderately differentiated	18	20	24
Poorly differentiated	97	132	117
Not assessable or missing	2	16	18
First-line chemotherapy included paclitaxel Units: Subjects			
Yes	104	151	149
No	13	20	15
Not available	1	3	0
Previous bevacizumab Units: Subjects			
Yes	6	9	9
No	112	165	155
Time since last chemotherapy Units: Subjects			
6-12 months	43	59	50
>12 months	75	115	114
Planned chemotherapy Units: Subjects			
Carboplatin alone	12	19	18
Carboplatin plus paclitaxel	89	130	121
Carboplatin plus gemcitabine	17	25	25
Time from first histological diagnosis to randomisation Units: weeks			
median	82.6	82.9	87.4
inter-quartile range (Q1-Q3)	60 to 117	64 to 135	65 to 117

Reporting group values	Total		
Number of subjects	456		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		

From 65-84 years	0		
85 years and over	0		

Age continuous Units: years median inter-quartile range (Q1-Q3)	- 		
Gender categorical Units: Subjects			
Female	456		
Male	0		
ECOG Status Units: Subjects			
Zero	273		
One	178		
Two	1		
Three	1		
Not available	3		
Primary tumour type Units: Subjects			
Ovary	368		
Fallopian	13		
Peritoneal	75		
Histology Units: Subjects			
Serous	332		
Endometrioid	19		
Clear cell	16		
Mucinous	4		
Mixed or other	77		
Undifferentiated	5		
Not available	3		
Tumour grade Units: Subjects			
Well differentiated	12		
Moderately differentiated	62		
Poorly differentiated	346		
Not assessable or missing	36		
First-line chemotherapy included paclitaxel Units: Subjects			
Yes	404		
No	48		
Not available	4		
Previous bevacizumab Units: Subjects			
Yes	24		
No	432		
Time since last chemotherapy Units: Subjects			
6-12 months	152		

>12 months	304		
Planned chemotherapy Units: Subjects			
Carboplatin alone	49		
Carboplatin plus paclitaxel	340		
Carboplatin plus gemcitabine	67		
Time from first histological diagnosis to randomisation Units: weeks			
median			
inter-quartile range (Q1-Q3)	-		

Subject analysis sets

Subject analysis set title	Reference + Concurrent
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This entry was created to accommodate a secondary analysis of Quality of Life outcomes.

Subject analysis set title	Concurrent + Maintenance
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This entry was created to accommodate a secondary analysis of Quality of Life outcomes.

Reporting group values	Reference + Concurrent	Concurrent + Maintenance	
Number of subjects	292	338	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical Units: Subjects			
Female			
Male			
ECOG Status Units: Subjects			
Zero			
One			
Two			
Three			

Not available			
Primary tumour type Units: Subjects			
Ovary Fallopian Peritoneal			
Histology Units: Subjects			
Serous Endometrioid Clear cell Mucinous Mixed or other Undifferentiated Not available			
Tumour grade Units: Subjects			
Well differentiated Moderately differentiated Poorly differentiated Not assessable or missing			
First-line chemotherapy included paclitaxel Units: Subjects			
Yes No Not available			
Previous bevacizumab Units: Subjects			
Yes No			
Time since last chemotherapy Units: Subjects			
6-12 months >12 months	83 189	109 229	
Planned chemotherapy Units: Subjects			
Carboplatin alone Carboplatin plus paclitaxel Carboplatin plus gemcitabine			
Time from first histological diagnosis to randomisation Units: weeks median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Reference
Reporting group description:	
6 cycles of platinum-based chemotherapy plus Placebo during chemotherapy	
Reporting group title	Concurrent
Reporting group description:	
6 cycles of platinum-based chemotherapy plus Cediranib during chemotherapy; then an oral daily placebo tablet up to 18 months from randomisation or until progression	
Reporting group title	Maintenance
Reporting group description:	
6 cycles of platinum-based chemotherapy plus Cediranib during chemotherapy; plus oral cediranib daily during chemotherapy and then continued up to 18 months from randomisation or until progression.	
Subject analysis set title	Reference + Concurrent
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This entry was created to accommodate a secondary analysis of Quality of Life outcomes.	
Subject analysis set title	Concurrent + Maintenance
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This entry was created to accommodate a secondary analysis of Quality of Life outcomes.	

Primary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)
End point description:	
End point type	Primary
End point timeframe:	
Progression-free survival was defi ned as time from randomisation to disease progression or death from any cause	

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118	174	164	
Units: month				
median (inter-quartile range (Q1-Q3))	8.7 (7.7 to 9.4)	9.9 (9.4 to 10.5)	11 (10.4 to 11.7)	

Statistical analyses

Statistical analysis title	PFS ; HR
Comparison groups	Maintenance v Reference

Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	0.72

Statistical analysis title	Restricted Mean Survival
Statistical analysis description:	
Analysis unit is months.	
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
Method	Restricted Mean Survival Time Difference
Parameter estimate	Restricted Mean Survival Time Difference
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.9
upper limit	4.4

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)[1]

End point description:

End point type	Primary

End point timeframe:

Progression-free survival was defined as time from randomisation to disease progression or death from any cause

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The outcome is reported for Arms A and B. Baseline statistics for Arm C are presented in a different outcome.

End point values	Reference	Concurrent		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	174		
Units: months				
median (inter-quartile range (Q1-Q3))	8.7 (7.7 to 9.4)	9.9 (9.4 to 10.5)		

Statistical analyses

Statistical analysis title	PFS ; HR
Comparison groups	Reference v Concurrent
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0036
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	0.89

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

End point type	Secondary

End point timeframe:

Overall survival (OS) is calculated from the date of randomisation to date of death from any cause

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	118	174	164	
Units: months				
median (inter-quartile range (Q1-Q3))	19.9 (17.4 to 26.5)	26.6 (22.6 to 29.1)	27.3 (24.8 to 33.0)	

Statistical analyses

Statistical analysis title	OS; HR
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.11

Statistical analysis title	Restricted Mean Survival; OS
Statistical analysis description:	
Analysis unit is months.	
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Restricted Mean Survival Time Difference
Point estimate	4.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	10.3

Secondary: QLQ C30	
End point title	QLQ C30
End point description:	

End point type	Secondary
End point timeframe:	
Baseline to 1 year of enrollment.	

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	126	132	
Units: points				
arithmetic mean (standard deviation)	-6.4 (± 28.0)	-0.7 (± 21.7)	-4.6 (± 20.9)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	4.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	11

Secondary: Improved Ascites Resolution During Chemotherapy

End point title	Improved Ascites Resolution During Chemotherapy[2]

End point description:

End point type	Secondary

End point timeframe:

From baseline to the end of chemotherapy.

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Physical function was explored in arms A and B/C combined.

End point values	Reference	Concurrent + Maintenance		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	39	113		
Units: points				
arithmetic mean (standard deviation)				
Baseline	37.1 (± 25.0)	34.9 (± 22.0)		
End of chemotherapy	24.2 (± 19.9)	21.4 (± 18.2)		

Statistical analyses

Statistical analysis title	Difference in the area under the curve
Comparison groups	Reference v Concurrent + Maintenance
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98 [3]
Method	Difference in the area under the curve

Notes:

[3] - Calculated using the difference in the area under the curve during chemotherapy adjusted for the baseline score

Secondary: Improved QoL: Global

End point title	Improved QoL: Global[4]

End point description:

End point type	Secondary

End point timeframe:

Baseline to chemotherapy midpoint (Week 9).

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Physical function was explored in arms A and B/C combined.

End point values	Reference	Concurrent + Maintenance		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	87	176		
Units: points				
arithmetic mean (standard deviation)				
Baseline	69.9 (± 20.2)	69.1 (± 21.3)		
Midpoint	64.0 (± 19.9)	65.8 (± 19.6)		

Statistical analyses

Statistical analysis title	Interaction test

Statistical analysis description:

Interaction test of the treatment group and whether or not the patient was symptomatic at enrollment

Comparison groups	Reference v Concurrent + Maintenance
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88
Method	Interaction test

Secondary: Improved QoL: Pain

End point title	Improved QoL: Pain[5]

End point description:

End point type	Secondary

End point timeframe:

Baseline to chemotherapy midpoint (week 9).

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Physical function was explored in arms A and B/C combined.

End point values	Reference	Concurrent + Maintenance		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	87	176		
Units: points				
arithmetic mean (standard deviation)				
Baseline	82.7 (± 19.6)	84.0 (± 17.9)		
Midpoint	75.0 (± 20.0)	78.0 (± 19.0)		

Statistical analyses

Statistical analysis title	Interaction Test

Statistical analysis description:

Interaction test of the treatment group and whether or not the patient was symptomatic at enrollment.

Comparison groups	Reference v Concurrent + Maintenance
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Interaction test

Secondary: Improved QoL: Physical function

End point title	Improved QoL: Physical function[6]

End point description:

End point type	Secondary

End point timeframe:

Baseline to chemotherapy midpoint (week 9).

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Physical function was explored in arms A and B/C combined.

End point values	Reference	Concurrent + Maintenance		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	87	176		
Units: points				
arithmetic mean (standard deviation)				
Baseline	23.2 (± 23.2)	22.0 (± 24.2)		
Midpoint	20.5 (± 23.9)	17.8 (± 22.6)		

Statistical analyses

Statistical analysis title	Interaction test

Statistical analysis description:

Interaction test of the treatment group and whether or not the patient was symptomatic at enrollment.

Comparison groups	Reference v Concurrent + Maintenance
Number of subjects included in analysis	263
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.63
Method	Interaction test

Secondary: Impaired fatigue during maintenance treatment

End point title	Impaired fatigue during maintenance treatment[7]

End point description:

End point type	Secondary

End point timeframe:

End of chemotherapy to 1 year.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Impaired fatigue was explored in arms A and B combined vs C.

End point values	Maintenance	Reference + Concurrent		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	84	140		
Units: points				
arithmetic mean (standard deviation)				
End of chemotherapy	74.2 (± 22.0)	72.0 (± 27.0)		
1 year	78.6 (± 27.3)	72.5 (± 30.8)		

Statistical analyses

Statistical analysis title	ANCOVA

Statistical analysis description:

Analysis of covariance adjusted for the 18-week score

Comparison groups	Maintenance v Reference + Concurrent
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.17
Method	ANCOVA

Secondary: Impaired social functioning during maintenance treatment

End point title	Impaired social functioning during maintenance treatment[8]

End point description:

End point type	Secondary

End point timeframe:

End of chemotherapy to 1 year.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Impaired social functioning was explored in arms A and B combined vs C.

End point values	Maintenance	Reference + Concurrent		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	84	140		
Units: points				
arithmetic mean (standard deviation)				
End of chemotherapy	38.0 (± 22.6)	37.6 (± 24.4)		
1 year	30.0 (± 25.2)	31.0 (± 25.5)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Maintenance v Reference + Concurrent
Number of subjects included in analysis	224
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	ANCOVA

Other pre-specified: Time to First Subsequent Treatment (TFST)

End point title	Time to First Subsequent Treatment (TFST)[9]

End point description:

End point type	Other pre-specified

End point timeframe:

exploratory outcome given its emerging clinical relevance, and the fact that patients could continue trial drug beyond documented disease progression

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This was only evaluated in the arms specified.

End point values	Reference	Maintenance		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	164		
Units: months				
median (inter-quartile range (Q1-Q3))	11.5 (10.4 to 12.4)	13.2 (12.0 to 15.1)		

Statistical analyses

Statistical analysis title	Restricted Mean Survival; TFST
Statistical analysis description:	
Analysis unit is months.	
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Restricted Mean Survival Time Difference
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	8.8

Statistical analysis title	Hazard Ratio
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0014
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.85

Other pre-specified: QLQ C30 Arm B vs Arm A

End point title	QLQ C30 Arm B vs Arm A

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline to 1 year enrollment.

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	126	132	
Units: points				
arithmetic mean (standard deviation)	-6.4 (± 28.0)	-0.7 (± 21.7)	-4.6 (± 20.9)	

Statistical analyses

Statistical analysis title	ANCOVA; Arm B vs Arm A
Comparison groups	Reference v Concurrent
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	8.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	14.9

Other pre-specified: QLQ C30 End of chemotherapy

End point title	QLQ C30 End of chemotherapy

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline to end of chemotherapy .

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	126	132	
Units: points				
arithmetic mean (confidence interval 95%)	-2.8 (-8.6 to 3.1)	-7.4 (-12.3 to -2.4)	-12.0 (-17.0 to -7.0)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA

Other pre-specified: QLQ C30 End of chemotherapy Arm B vs Arm A

End point title	QLQ C30 End of chemotherapy Arm B vs Arm A

End point description:

End point type	Other pre-specified

End point timeframe:

Baseline to end of chemotherapy .

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	126	132	
Units: points				
arithmetic mean (confidence interval 95%)	-2.8 (-8.6 to 3.1)	-7.4 (-12.3 to -2.4)	-12.0 (-17.0 to -7.0)	

Statistical analyses

Statistical analysis title	ANCOVA; Arm B vs Arm A
Comparison groups	Reference v Concurrent
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	ANCOVA

Other pre-specified: QLQ C30 End of chemotherapy to year 1	
End point title	QLQ C30 End of chemotherapy to year 1
End point description:	

End point type	Other pre-specified
End point timeframe:	
End of chemotherapy to 1 year.	

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	126	132	
Units: points				
arithmetic mean (confidence interval 95%)	-1.0 (-5.4 to 3.5)	5.5 (1.6 to 9.3)	2.5 (-1.3 to 6.3)	

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	Reference v Maintenance
Number of subjects included in analysis	214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	ANCOVA

Other pre-specified: QLQ C30 End of chemotherapy to 1 year Arm B vs Arm A	
End point title	QLQ C30 End of chemotherapy to 1 year Arm B vs Arm A
End point description:	

End point type	Other pre-specified
End point timeframe:	
End of chemotherapy to 1 year.	

End point values	Reference	Concurrent	Maintenance	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	82	126	132	
Units: points				
arithmetic mean (confidence interval 95%)	-1.0 (-5.4 to 3.5)	5.5 (1.6 to 9.3)	2.5 (-1.3 to 6.3)	

Statistical analyses

Statistical analysis title	ANCOVA; Arm B vs Arm A
Comparison groups	Reference v Concurrent
Number of subjects included in analysis	208
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	ANCOVA

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	CMaintenance
Reporting group description: -	
Reporting group title	BConcurrent
Reporting group description: -	
Reporting group title	AReference
Reporting group description: -	

Serious adverse events	CMaintenance	BConcurrent	AReference
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 164 (32.32%)	48 / 174 (27.59%)	34 / 118 (28.81%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Flushing	Additional description: Flushing		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (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
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 164 (0.61%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Edema - head and neck	Additional description: Edema - head and neck		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (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
Fever	Additional description: Fever		

subjects affected / exposed	2 / 164 (1.22%)	5 / 174 (2.87%)	4 / 118 (3.39%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Flu-like syndrome	Additional description: Flu-like syndrome		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - Chest wall	Additional description: Pain - Chest wall		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (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
Rigors/chills	Additional description: Rigors/chills		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Hemorrhage/Bleeding (tumour site)	Additional description: Hemorrhage/Bleeding (tumour site)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm	Additional description: Bronchospasm		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Cough	Additional description: Cough		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnea	Additional description: Dyspnea		
subjects affected / exposed	10 / 164 (6.10%)	8 / 174 (4.60%)	4 / 118 (3.39%)
occurrences causally related to treatment / all	0 / 15	0 / 8	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hemorrhage, Nose	Additional description: Hemorrhage, Nose		
subjects affected / exposed	1 / 164 (0.61%)	3 / 174 (1.72%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	4 / 164 (2.44%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary - Other (chest tightness)	Additional description: Pulmonary - Other (chest tightness)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Pulmonary/Upper Respiratory - other (nasal septal perforation)	Additional description: Pulmonary/Upper Respiratory - other (nasal septal perforation)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Psychiatric disorders			
Confusion	Additional description: Confusion		
subjects affected / exposed	0 / 164 (0.00%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia	Additional description: Insomnia		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Mood alteration	Additional description: Mood alteration		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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

Mood alteration - Depression	Additional description: Mood alteration - Depression		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Investigations			
Creatinine	Additional description: Creatinine		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Creatinine; Hemoglobin	Additional description: Creatinine; Hemoglobin		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Injury, poisoning and procedural complications			
Bruising	Additional description: Bruising		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Fracture	Additional description: Fracture		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis/embolism (vascular access-related)	Additional description: Thrombosis/embolism (vascular access-related)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Wound complication, non-infectious	Additional description: Wound complication, non-infectious		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac ischemia/infarction	Additional description: Cardiac ischemia/infarction		

subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Pain - Cardiac/heart	Additional description: Pain - Cardiac/heart		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Sinus Tachycardia	Additional description: Sinus Tachycardia		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CNS cerebrovascular ischemia	Additional description: CNS cerebrovascular ischemia		
subjects affected / exposed	5 / 164 (3.05%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CNS ischemia	Additional description: CNS ischemia		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Dizziness	Additional description: Dizziness		
subjects affected / exposed	4 / 164 (2.44%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy	Additional description: Neuropathy		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathy: cranial	Additional description: Neuropathy: cranial		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - Head/headache	Additional description: Pain - Head/headache		

subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	0 / 118 (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
Seizure	Additional description: Seizure		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence	Additional description: Somnolence		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence/depressed level of consciousness	Additional description: Somnolence/depressed level of consciousness		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Speech impairment	Additional description: Speech impairment		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Syncope (fainting)	Additional description: Syncope (fainting)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tremor	Additional description: Tremor		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	0 / 118 (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
Vasovagal episode	Additional description: Vasovagal episode		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Blood and lymphatic system disorders			
Hemolysis	Additional description: Hemolysis		

subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Auditory/Ear - other (perforated ear drum)	Additional description: Auditory/Ear - other (perforated ear drum)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Gastrointestinal disorders			
Ascites	Additional description: Ascites		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Diarrhea and Febrile neutropenia	Additional description: Diarrhea and Febrile neutropenia		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhea; Vomiting	Additional description: Diarrhea; Vomiting		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (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
Distension	Additional description: Distension		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Distension/bloating, abdominal	Additional description: Distension/bloating, abdominal		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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

Enteritis	Additional description: Enteritis		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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

Fistula	Additional description: Fistula		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Flatulence	Additional description: Flatulence		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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

Haemorrhage, Upper GI	Additional description: Haemorrhage, Upper GI		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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

Heartburn	Additional description: Heartburn		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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

Hemorrhage, GI	Additional description: Hemorrhage, GI		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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

Hemorrhage, GI - Stomach	Additional description: Hemorrhage, GI - Stomach		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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

Hemorrhage, Rectum	Additional description: Hemorrhage, Rectum		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ileus	Additional description: Ileus

subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Mucositis/stomatitis	Additional description: Mucositis/stomatitis		
subjects affected / exposed	4 / 164 (2.44%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mucositis/stomatitis - oral cavity	Additional description: Mucositis/stomatitis - oral cavity		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Nausea and Vomiting	Additional description: Nausea and Vomiting		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (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
Nausea; Vomiting	Additional description: Nausea; Vomiting		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Obstruction, GI	Additional description: Obstruction, GI		
subjects affected / exposed	3 / 164 (1.83%)	2 / 174 (1.15%)	2 / 118 (1.69%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction, GI - ileum	Additional description: Obstruction, GI - ileum		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - Gastrointestinal - Abdomen	Additional description: Pain - Gastrointestinal - Abdomen		
subjects affected / exposed	4 / 164 (2.44%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - Gastrointestinal - Abdomen NOS	Additional description: Pain - Gastrointestinal - Abdomen NOS		

subjects affected / exposed	7 / 164 (4.27%)	10 / 174 (5.75%)	7 / 118 (5.93%)
occurrences causally related to treatment / all	0 / 7	0 / 12	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis	Additional description: Pancreatitis		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Ulcer, GI - Anus	Additional description: Ulcer, GI - Anus		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Ulcer, GI - Duodenum	Additional description: Ulcer, GI - Duodenum		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Hepatobiliary disorders			
Liver dysfunction	Additional description: Liver dysfunction		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus	Additional description: Pruritus		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash; Vomiting	Additional description: Rash; Vomiting		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Urticaria	Additional description: Urticaria		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Pain - Other (Dysuria)	Additional description: Pain - Other (Dysuria)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Renal failure	Additional description: Renal failure		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
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			
Arthritis	Additional description: Arthritis		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Muscle weakness	Additional description: Muscle weakness		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Pain - Back	Additional description: Pain - Back		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain - Bone	Additional description: Pain - Bone		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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 - Extremity-limb	Additional description: Pain - Extremity-limb		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	0 / 118 (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
Infections and infestations			
Infection - Bladder (urinary)	Additional description: Infection - Bladder (urinary)		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection - Bronchus	Additional description: Infection - Bronchus		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection - General - Catheter related	Additional description: Infection - General - Catheter related		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection - Lung	Additional description: Infection - Lung		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection - Lung (pneumonia)	Additional description: Infection - Lung (pneumonia)		
subjects affected / exposed	0 / 164 (0.00%)	3 / 174 (1.72%)	3 / 118 (2.54%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection - Other (abscess)	Additional description: Infection - Other (abscess)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infection - Pelvis NOS	Additional description: Infection - Pelvis NOS		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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

Infection - Peritoneal cavity	Additional description: Infection - Peritoneal cavity		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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

Infection - Skin (cellulitis)	Additional description: Infection - Skin (cellulitis)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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

Infection - Small bowel NOS	Additional description: Infection - Small bowel NOS

subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (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
Infection - Upper airway	Additional description: Infection - Upper airway		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Infection (documented clinically) with Grade 3 or 4 ANC	Additional description: Infection (documented clinically) with Grade 3 or 4 ANC		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (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
Infection with unknown ANC	Additional description: Infection with unknown ANC		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypomagnesemia	Additional description: Hypomagnesemia		
subjects affected / exposed	3 / 164 (1.83%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatremia	Additional description: Hyponatremia		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	CMaintenance	BConcurrent	AReference
Total subjects affected by non-serious adverse events			
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
Vascular disorders			
Flushing	Additional description: Flushing		

subjects affected / exposed	8 / 164 (4.88%)	7 / 174 (4.02%)	2 / 118 (1.69%)
occurrences (all)	16	9	2
Haemmorhage/Bleeding	Additional description: Haemmorhage/Bleeding		
subjects affected / exposed	6 / 164 (3.66%)	9 / 174 (5.17%)	2 / 118 (1.69%)
occurrences (all)	7	20	2
Haemmorhage/Bleeding (1)	Additional description: Haemmorhage/Bleeding (1)		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Haemmorhage/Bleeding (2)	Additional description: Haemmorhage/Bleeding (2)		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Hematoma	Additional description: Hematoma		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	2	0	2
Hot flashes	Additional description: Hot flashes		
subjects affected / exposed	8 / 164 (4.88%)	12 / 174 (6.90%)	14 / 118 (11.86%)
occurrences (all)	30	27	69
Hypertension	Additional description: Hypertension		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1509	1568	1039
Hypotension	Additional description: Hypotension		
subjects affected / exposed	5 / 164 (3.05%)	6 / 174 (3.45%)	3 / 118 (2.54%)
occurrences (all)	6	7	6
Phlebitis	Additional description: Phlebitis		
subjects affected / exposed	5 / 164 (3.05%)	2 / 174 (1.15%)	4 / 118 (3.39%)
occurrences (all)	6	2	6
Thrombophlebitis	Additional description: Thrombophlebitis		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Thrombosis/thrombus/embolism	Additional description: Thrombosis/thrombus/embolism		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1515	1575	1039
Vascular - Other (insufficiency)	Additional description: Vascular - Other (insufficiency)		

subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Vascular - Other (raynaud's disease)	Additional description: Vascular - Other (raynaud's disease)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	11
General disorders and administration site conditions			
Constitutional Symptoms - Other (cold extremities)	Additional description: Constitutional Symptoms - Other (cold extremities)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	1	0
Constitutional Symptoms - Other (fall)	Additional description: Constitutional Symptoms - Other (fall)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Constitutional Symptoms - Other (Fear of going out)	Additional description: Constitutional Symptoms - Other (Fear of going out)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Constitutional Symptoms - Other (forgetfulness)	Additional description: Constitutional Symptoms - Other (forgetfulness)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Constitutional Symptoms - Other (Light headed)	Additional description: Constitutional Symptoms - Other (Light headed)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Constitutional Symptoms - Other (psychological effects)	Additional description: Constitutional Symptoms - Other (psychological effects)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Constitutional Symptoms - Other (restlessness)	Additional description: Constitutional Symptoms - Other (restlessness)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Constitutional Symptoms - Other (warm feet)	Additional description: Constitutional Symptoms - Other (warm feet)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Edema	Additional description: Edema		

subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	1	3	2
Edema: head and neck	Additional description: Edema: head and neck		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences (all)	2	3	2
Edema: limb	Additional description: Edema: limb		
subjects affected / exposed	14 / 164 (8.54%)	22 / 174 (12.64%)	6 / 118 (5.08%)
occurrences (all)	38	44	11
Edema: trunk/genital	Additional description: Edema: trunk/genital		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	6	3	0
Fatigue	Additional description: Fatigue		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1518	1577	1041
Fever	Additional description: Fever		
subjects affected / exposed	6 / 164 (3.66%)	11 / 174 (6.32%)	5 / 118 (4.24%)
occurrences (all)	7	11	9
Flu-like syndrome	Additional description: Flu-like syndrome		
subjects affected / exposed	6 / 164 (3.66%)	3 / 174 (1.72%)	9 / 118 (7.63%)
occurrences (all)	11	3	12
Gait/walking	Additional description: Gait/walking		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	3 / 118 (2.54%)
occurrences (all)	2	4	16
Injection site reaction	Additional description: Injection site reaction		
subjects affected / exposed	4 / 164 (2.44%)	5 / 174 (2.87%)	2 / 118 (1.69%)
occurrences (all)	10	7	3
Injection site reaction/Extravasation	Additional description: Injection site reaction/Extravasation		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pain	Additional description: Pain		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1513	1565	1040
Pain - Chest	Additional description: Pain - Chest		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	4	1	0

Pain - Chest/thorax NOS	Additional description: Pain - Chest/thorax NOS		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	4	1	3
Pain - Face	Additional description: Pain - Face		
subjects affected / exposed	3 / 164 (1.83%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	3	1	0
Pain - General	Additional description: Pain - General		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pain - General - Foreign body	Additional description: Pain - General - Foreign body		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	2	2	0
Pain - NOS	Additional description: Pain - NOS		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	3	0	0
Pain - Other (throat spasm)	Additional description: Pain - Other (throat spasm)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Pain NOS	Additional description: Pain NOS		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Rigors/chills	Additional description: Rigors/chills		
subjects affected / exposed	4 / 164 (2.44%)	3 / 174 (1.72%)	5 / 118 (4.24%)
occurrences (all)	4	3	10
Immune system disorders			
Allergic reaction	Additional description: Allergic reaction		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1537	1584	1056
Cytokine release syndrome	Additional description: Cytokine release syndrome		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Haemorrhage, GU - Urinary NOS	Additional description: Haemorrhage, GU - Urinary NOS		
subjects affected / exposed	2 / 164 (1.22%)	5 / 174 (2.87%)	0 / 118 (0.00%)
occurrences (all)	4	5	0
Haemorrhage, GU - Vagina	Additional description: Haemorrhage, GU - Vagina		

subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	1	0
Infection - Sexual/reproductive function	Additional description: Infection - Sexual/reproductive function		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Irregular menses	Additional description: Irregular menses		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pain - Breast	Additional description: Pain - Breast		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	3 / 118 (2.54%)
occurrences (all)	1	12	5
Pain - Pelvis	Additional description: Pain - Pelvis		
subjects affected / exposed	3 / 164 (1.83%)	3 / 174 (1.72%)	3 / 118 (2.54%)
occurrences (all)	4	8	6
Pain - Perineum	Additional description: Pain - Perineum		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	1	1
Sexual - Other (vaginal prolapse)	Additional description: Sexual - Other (vaginal prolapse)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	1	0	3
Sexual - Other (vulval irritation)	Additional description: Sexual - Other (vulval irritation)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Vaginal discharge	Additional description: Vaginal discharge		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	3	5	0
Vaginal dryness	Additional description: Vaginal dryness		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	5	4	3
Respiratory, thoracic and mediastinal disorders			
Airway obstruction - Bronchus	Additional description: Airway obstruction - Bronchus		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Apnea	Additional description: Apnea		

subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	7
Bronchospasm	Additional description: Bronchospasm		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	7	1	15
Bronchospasm, wheezing	Additional description: Bronchospasm, wheezing		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences (all)	1	0	2
Cough	Additional description: Cough		
subjects affected / exposed	36 / 164 (21.95%)	32 / 174 (18.39%)	28 / 118 (23.73%)
occurrences (all)	78	50	60
Dyspnea	Additional description: Dyspnea		
subjects affected / exposed	59 / 164 (35.98%)	66 / 174 (37.93%)	34 / 118 (28.81%)
occurrences (all)	209	189	123
Haemorrhage pulmonary - Bronchopulmonary NOS	Additional description: Haemorrhage pulmonary - Bronchopulmonary NOS		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Haemorrhage pulmonary - Nose	Additional description: Haemorrhage pulmonary - Nose		
subjects affected / exposed	3 / 164 (1.83%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	3	0	0
Nasal/paranasal reactions	Additional description: Nasal/paranasal reactions		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	3 / 118 (2.54%)
occurrences (all)	2	2	13
Pain - Oral cavity	Additional description: Pain - Oral cavity		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Pain - Pleura	Additional description: Pain - Pleura		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Pain - Throat	Additional description: Pain - Throat		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Pain - Throat/pharynx/larynx	Additional description: Pain - Throat/pharynx/larynx		
subjects affected / exposed	14 / 164 (8.54%)	13 / 174 (7.47%)	11 / 118 (9.32%)
occurrences (all)	25	18	19

Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences (all)	6	0	2
Pulmonary - Other (chest tightness)	Additional description: Pulmonary - Other (chest tightness)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Pulmonary - Other (throat irritation)	Additional description: Pulmonary - Other (throat irritation)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pulmonary - Other (tonsillar erythema)	Additional description: Pulmonary - Other (tonsillar erythema)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Rhinitis	Additional description: Rhinitis		
subjects affected / exposed	14 / 164 (8.54%)	13 / 174 (7.47%)	3 / 118 (2.54%)
occurrences (all)	30	26	13
Voice changes	Additional description: Voice changes		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1548	1580	1045
Psychiatric disorders			
Confusion	Additional description: Confusion		
subjects affected / exposed	2 / 164 (1.22%)	5 / 174 (2.87%)	2 / 118 (1.69%)
occurrences (all)	2	5	3
Insomnia	Additional description: Insomnia		
subjects affected / exposed	25 / 164 (15.24%)	37 / 174 (21.26%)	20 / 118 (16.95%)
occurrences (all)	99	142	127
Mood alteration	Additional description: Mood alteration		
subjects affected / exposed	6 / 164 (3.66%)	5 / 174 (2.87%)	0 / 118 (0.00%)
occurrences (all)	13	7	0
Mood alteration - Agitation	Additional description: Mood alteration - Agitation		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	2	2	0
Mood alteration - Anxiety	Additional description: Mood alteration - Anxiety		
subjects affected / exposed	13 / 164 (7.93%)	16 / 174 (9.20%)	15 / 118 (12.71%)
occurrences (all)	58	52	52
Mood alteration - Depression	Additional description: Mood alteration - Depression		

subjects affected / exposed	19 / 164 (11.59%)	13 / 174 (7.47%)	13 / 118 (11.02%)
occurrences (all)	50	38	44
Other - Vivid dreams	Additional description: Other - Vivid dreams		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Psychosis	Additional description: Psychosis		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	1	0	1
Investigations			
Alkaline phosphatase	Additional description: Alkaline phosphatase		
subjects affected / exposed	23 / 164 (14.02%)	28 / 174 (16.09%)	10 / 118 (8.47%)
occurrences (all)	55	84	27
ALT or AST	Additional description: ALT or AST		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1509	1568	1037
APTT	Additional description: APTT		
subjects affected / exposed	162 / 164 (98.78%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1420	1477	980
AST	Additional description: AST		
subjects affected / exposed	3 / 164 (1.83%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	3	1	1
Bilirubin	Additional description: Bilirubin		
subjects affected / exposed	6 / 164 (3.66%)	4 / 174 (2.30%)	4 / 118 (3.39%)
occurrences (all)	10	13	10
Cholesterol	Additional description: Cholesterol		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	4 / 118 (3.39%)
occurrences (all)	11	6	17
Coagulation - Other (PT elevation)	Additional description: Coagulation - Other (PT elevation)		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences (all)	0	2	1
CPK	Additional description: CPK		
subjects affected / exposed	163 / 164 (99.39%)	174 / 174 (100.00%)	115 / 118 (97.46%)
occurrences (all)	1448	1501	991
Creatinine	Additional description: Creatinine		

subjects affected / exposed	11 / 164 (6.71%)	17 / 174 (9.77%)	7 / 118 (5.93%)
occurrences (all)	22	26	7
Fibrinogen	Additional description: Fibrinogen		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
GGT	Additional description: GGT		
subjects affected / exposed	7 / 164 (4.27%)	11 / 174 (6.32%)	2 / 118 (1.69%)
occurrences (all)	13	35	5
INR	Additional description: INR		
subjects affected / exposed	163 / 164 (99.39%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1439	1493	993
Leukocytes	Additional description: Leukocytes		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1552	1614	1079
Lymphopenia	Additional description: Lymphopenia		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	3 / 118 (2.54%)
occurrences (all)	1	4	3
Metabolic/Laboratory - Other (glycosuria)	Additional description: Metabolic/Laboratory - Other (glycosuria)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Metabolic/Laboratory - Other (high bicarbonate)	Additional description: Metabolic/Laboratory - Other (high bicarbonate)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	2	0
Metabolic/Laboratory - Other (high chloride)	Additional description: Metabolic/Laboratory - Other (high chloride)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	2	0
Metabolic/Laboratory - Other (high CRP)	Additional description: Metabolic/Laboratory - Other (high CRP)		
subjects affected / exposed	2 / 164 (1.22%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	2	3	1
Metabolic/Laboratory - Other (high globulins)	Additional description: Metabolic/Laboratory - Other (high globulins)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	1	0
Metabolic/Laboratory - Other (high	Additional description: Metabolic/Laboratory - Other (high LDH)		

LDH)			
subjects affected / exposed	1 / 164 (0.61%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	1	4	7
Metabolic/Laboratory - Other (high urea)	Additional description: Metabolic/Laboratory - Other (high urea)		
subjects affected / exposed	4 / 164 (2.44%)	7 / 174 (4.02%)	6 / 118 (5.08%)
occurrences (all)	7	9	13
Metabolic/Laboratory - Other (hyperphosphatemia)	Additional description: Metabolic/Laboratory - Other (hyperphosphatemia)		
subjects affected / exposed	5 / 164 (3.05%)	4 / 174 (2.30%)	1 / 118 (0.85%)
occurrences (all)	9	4	2
Metabolic/Laboratory - Other (ketonuria)	Additional description: Metabolic/Laboratory - Other (ketonuria)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Metabolic/Laboratory - Other (low chloride)	Additional description: Metabolic/Laboratory - Other (low chloride)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	2	0
Metabolic/Laboratory - Other (low GFR)	Additional description: Metabolic/Laboratory - Other (low GFR)		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	1	2	0
Metabolic/Laboratory - Other (low protein)	Additional description: Metabolic/Laboratory - Other (low protein)		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	0	7	0
Neutrophils	Additional description: Neutrophils		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1516	1571	1039
Platelets	Additional description: Platelets		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1513	1572	1038
Weight gain	Additional description: Weight gain		
subjects affected / exposed	1 / 164 (0.61%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	1	11	1
Weight loss	Additional description: Weight loss		

subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1519	1582	1038
Injury, poisoning and procedural complications			
Bruising	Additional description: Bruising		
subjects affected / exposed	7 / 164 (4.27%)	8 / 174 (4.60%)	1 / 118 (0.85%)
occurrences (all)	10	8	1
Fracture	Additional description: Fracture		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	3 / 118 (2.54%)
occurrences (all)	2	0	5
Infection - Wound	Additional description: Infection - Wound		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	2
Intra-op injury	Additional description: Intra-op injury		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Intraop Injury - Eye NOS	Additional description: Intraop Injury - Eye NOS		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Intraop Injury - Teeth	Additional description: Intraop Injury - Teeth		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Vein injury - Extremity-lower	Additional description: Vein injury - Extremity-lower		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Wound complications	Additional description: Wound complications		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Cardiac disorders			
Cardiac Arrhythmia	Additional description: Cardiac Arrhythmia		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Cardiac Arrhythmia - Sinus bradycardia	Additional description: Cardiac Arrhythmia - Sinus bradycardia		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0

Cardiac Arrhythmia - Sinus tachycardia	Additional description: Cardiac Arrhythmia - Sinus tachycardia		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Cardiac Arrhythmia - Tachycardia	Additional description: Cardiac Arrhythmia - Tachycardia		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	2 / 118 (1.69%)
occurrences (all)	1	2	2
Cardiac General - Other (ECG changes)	Additional description: Cardiac General - Other (ECG changes)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	6	0	1
Cardiac ischaemia/infarction	Additional description: Cardiac ischaemia/infarction		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1566	1047
LVSD	Additional description: LVSD		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Pain - Cardiac/heart	Additional description: Pain - Cardiac/heart		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	3	0	0
Palpitations	Additional description: Palpitations		
subjects affected / exposed	4 / 164 (2.44%)	4 / 174 (2.30%)	3 / 118 (2.54%)
occurrences (all)	6	10	3
Nervous system disorders			
Cerebrovascular ischemia	Additional description: Cerebrovascular ischemia		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1509	1567	1037
CNS ischaemia	Additional description: CNS ischaemia		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Dizziness	Additional description: Dizziness		
subjects affected / exposed	29 / 164 (17.68%)	23 / 174 (13.22%)	13 / 118 (11.02%)
occurrences (all)	58	53	23
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037

Involuntary movement	Additional description: Involuntary movement		
subjects affected / exposed	1 / 164 (0.61%)	3 / 174 (1.72%)	2 / 118 (1.69%)
occurrences (all)	1	15	2
Leukoencephalopathy	**Additional description: Leukoencephalopathy**		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1566	1037
Memory impairment	**Additional description: Memory impairment**		
subjects affected / exposed	4 / 164 (2.44%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	7	5	0
Neurology - Other (Bell's palsy)	**Additional description: Neurology - Other (Bell's palsy)**		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	3	0
Neurology - other (dysthesia)	**Additional description: Neurology - other (dysthesia)**		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Neurology - Other (Impaired concentration)	**Additional description: Neurology - Other (Impaired concentration)**		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Neurology - Other (Oral cavity dysthesia)	**Additional description: Neurology - Other (Oral cavity dysthesia)**		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Neurology - Other (Parkinsonism)	**Additional description: Neurology - Other (Parkinsonism)**		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Neuropathy-sensory	**Additional description: Neuropathy-sensory**		
subjects affected / exposed	5 / 164 (3.05%)	9 / 174 (5.17%)	6 / 118 (5.08%)
occurrences (all)	10	19	18
Neuropathy - motor	**Additional description: Neuropathy - motor**		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1507	1566	1037
Neuropathy - sensory	**Additional description: Neuropathy - sensory**		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1514	1566	1038
Neuropathy: Cranial	**Additional description: Neuropathy: Cranial**		

subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Neuropathy: cranial - Motor-jaw muscles; Sensory-facial	Additional description: Neuropathy: cranial - Motor-jaw muscles; Sensory-facial		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Neuropathy:cranial III Palsy	Additional description: Neuropathy:cranial III Palsy		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Pain - Head/headache	Additional description: Pain - Head/headache		
subjects affected / exposed	20 / 164 (12.20%)	25 / 174 (14.37%)	13 / 118 (11.02%)
occurrences (all)	55	58	26
Pain - Neuralgia/peripheral nerve	Additional description: Pain - Neuralgia/peripheral nerve		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pain - Neurology - headache	Additional description: Pain - Neurology - headache		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences (all)	0	2	2
Seizure	Additional description: Seizure		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Somnolence	Additional description: Somnolence		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	2	2	0
Speech impairment	Additional description: Speech impairment		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Syncope (fainting)	Additional description: Syncope (fainting)		
subjects affected / exposed	1 / 164 (0.61%)	3 / 174 (1.72%)	2 / 118 (1.69%)
occurrences (all)	2	3	3
Taste alteration	Additional description: Taste alteration		
subjects affected / exposed	27 / 164 (16.46%)	26 / 174 (14.94%)	11 / 118 (9.32%)
occurrences (all)	87	86	33
Tremor	Additional description: Tremor		
subjects affected / exposed	6 / 164 (3.66%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	9	4	3

Vasovagal episode	Additional description: Vasovagal episode		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	3 / 118 (2.54%)
occurrences (all)	0	2	3
Blood and lymphatic system disorders			
Blood	Additional description: Blood		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Blood - Other (Basophils)	Additional description: Blood - Other (Basophils)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Blood - Other (Lymphocytes)	Additional description: Blood - Other (Lymphocytes)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Blood - Other (mean corpuscular hemoglobin)	Additional description: Blood - Other (mean corpuscular hemoglobin)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Blood - Other (raising CA125)	Additional description: Blood - Other (raising CA125)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Blood/Bone marrow - Other (high mcv)	Additional description: Blood/Bone marrow - Other (high mcv)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	1	2	3
Blood/Bone marrow - Other (low iron)	Additional description: Blood/Bone marrow - Other (low iron)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	4	0	0
Blood/Bone marrow - Other (low pcv)	Additional description: Blood/Bone marrow - Other (low pcv)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Blood/Bone marrow - Other (low red cell count)	Additional description: Blood/Bone marrow - Other (low red cell count)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	2	3	0
Blood/Bone marrow - Other (RDW)	Additional description: Blood/Bone marrow - Other (RDW)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	2	3	0

Blood/Bone Marrow other esoinophils	Additional description: Blood/Bone Marrow other esoinophils		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Blood/Bone Marrow other RBC	Additional description: Blood/Bone Marrow other RBC		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	2
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1521	1573	1041
Haemoglobin	Additional description: Haemoglobin		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1519	1576	1058
Lymphatics	Additional description: Lymphatics		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Ear and labyrinth disorders			
Auditory/Ear	Additional description: Auditory/Ear		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1038
Auditory/Ear - Hearing loss	Additional description: Auditory/Ear - Hearing loss		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences (all)	1	0	2
Auditory/Ear - Other (Blocked ear)	Additional description: Auditory/Ear - Other (Blocked ear)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Auditory/Ear - Other (Muffled hearing)	Additional description: Auditory/Ear - Other (Muffled hearing)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Pain - Ear	Additional description: Pain - Ear		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	2	0	3
Pain - External ear	Additional description: Pain - External ear		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1

Tinnitus	Additional description: Tinnitus		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	7	3
Eye disorders			
Blurred vision	Additional description: Blurred vision		
subjects affected / exposed	10 / 164 (6.10%)	6 / 174 (3.45%)	8 / 118 (6.78%)
occurrences (all)	21	17	19
Cataract	Additional description: Cataract		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	4	1	1
Diplopia	Additional description: Diplopia		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	3	1	0
Dry eye	Additional description: Dry eye		
subjects affected / exposed	2 / 164 (1.22%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	4	12	1
Flashing lights	Additional description: Flashing lights		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	3	1	0
Glaucoma	Additional description: Glaucoma		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	15	0	0
Ocular - Other (impaired vision)	Additional description: Ocular - Other (impaired vision)		
subjects affected / exposed	3 / 164 (1.83%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	4	7	2
Ocular - Other (Itchy eyes)	Additional description: Ocular - Other (Itchy eyes)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Ocular - Other (pruritus)	Additional description: Ocular - Other (pruritus)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Ocular - Other (visual changes)	Additional description: Ocular - Other (visual changes)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	0	1	2
Ocular surface disease	Additional description: Ocular surface disease		

subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	1	1
Retinal detachment	Additional description: Retinal detachment		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Watery eye	Additional description: Watery eye		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	19	1	2
Gastrointestinal disorders			
Ascites	Additional description: Ascites		
subjects affected / exposed	6 / 164 (3.66%)	2 / 174 (1.15%)	4 / 118 (3.39%)
occurrences (all)	14	7	5
Cheilitis	Additional description: Cheilitis		
subjects affected / exposed	2 / 164 (1.22%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	3	1	1
Constipation	Additional description: Constipation		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1511	1568	1040
Dental	Additional description: Dental		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Dental: Teeth	Additional description: Dental: Teeth		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Diarrhea	Additional description: Diarrhea		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	3	0
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1518	1595	1043
Distension	Additional description: Distension		
subjects affected / exposed	17 / 164 (10.37%)	33 / 174 (18.97%)	25 / 118 (21.19%)
occurrences (all)	40	84	58
Dry mouth	Additional description: Dry mouth		

subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1509	1569	1037
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	3 / 164 (1.83%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	6	3	2
Esophagitis	Additional description: Esophagitis		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	1	1	1
Fistula, GI	Additional description: Fistula, GI		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Fistula, GU - Vagina	Additional description: Fistula, GU - Vagina		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Flatulence	Additional description: Flatulence		
subjects affected / exposed	11 / 164 (6.71%)	12 / 174 (6.90%)	7 / 118 (5.93%)
occurrences (all)	32	41	14
Gastritis	Additional description: Gastritis		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	1	1
Gastrointestinal - Other (Altered bowel function)	Additional description: Gastrointestinal - Other (Altered bowel function)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	1	2
Gastrointestinal - Other (Increased appetite)	Additional description: Gastrointestinal - Other (Increased appetite)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	3 / 118 (2.54%)
occurrences (all)	0	0	5
Gastrointestinal - Other (Irritable bowel)	Additional description: Gastrointestinal - Other (Irritable bowel)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	6	0
Gastrointestinal - Other (Ructus)	Additional description: Gastrointestinal - Other (Ructus)		

subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	3 / 118 (2.54%)
occurrences (all)	5	0	4
GI - Other (hernia)	Additional description: GI - Other (hernia)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
GI - Other (Hiatus hernia)	Additional description: GI - Other (Hiatus hernia)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	4	0	4
GI - Other (Increased appetite)	Additional description: GI - Other (Increased appetite)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
GI - Other (rectal urgency)	Additional description: GI - Other (rectal urgency)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Haemorrhage, GI - Upper GI	Additional description: Haemorrhage, GI - Upper GI		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	2	1	0
Heartburn	Additional description: Heartburn		
subjects affected / exposed	25 / 164 (15.24%)	33 / 174 (18.97%)	24 / 118 (20.34%)
occurrences (all)	59	68	58
Hemorrhoids	Additional description: Hemorrhoids		
subjects affected / exposed	4 / 164 (2.44%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	7	4	1
Ileum	Additional description: Ileum		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Ileus	Additional description: Ileus		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	1	1
Incontinence, anal	Additional description: Incontinence, anal		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Mucositis	Additional description: Mucositis		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1528	1584	1044

Mucositis - Oral cavity	Additional description: Mucositis - Oral cavity		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Nausea	Additional description: Nausea		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1514	1575	1042
Obstruction, GI	Additional description: Obstruction, GI		
subjects affected / exposed	3 / 164 (1.83%)	2 / 174 (1.15%)	4 / 118 (3.39%)
occurrences (all)	4	3	4
Obstruction, GI - Colon	Additional description: Obstruction, GI - Colon		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	3	1	0
Pain - Abdomen NOS	Additional description: Pain - Abdomen NOS		
subjects affected / exposed	36 / 164 (21.95%)	38 / 174 (21.84%)	27 / 118 (22.88%)
occurrences (all)	81	68	67
Pain - Anus	Additional description: Pain - Anus		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	1	2	0
Pain - Dental/teeth/peridontal	Additional description: Pain - Dental/teeth/peridontal		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	4	1
Pain - Gastrointestinal	Additional description: Pain - Gastrointestinal		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pain - Lip	Additional description: Pain - Lip		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Pain - Oral-gums	Additional description: Pain - Oral-gums		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	4	0	0
Pain - Oral cavity	Additional description: Pain - Oral cavity		
subjects affected / exposed	5 / 164 (3.05%)	10 / 174 (5.75%)	1 / 118 (0.85%)
occurrences (all)	14	21	1
Pain - Rectum	Additional description: Pain - Rectum		

subjects affected / exposed	5 / 164 (3.05%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	6	4	0
Pain - Stomach	Additional description: Pain - Stomach		
subjects affected / exposed	9 / 164 (5.49%)	2 / 174 (1.15%)	5 / 118 (4.24%)
occurrences (all)	16	3	9
Perforation, GI	Additional description: Perforation, GI		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1566	1037
Periodontal	Additional description: Periodontal		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Salivary gland changes	Additional description: Salivary gland changes		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	5	3	0
Ulcer, GI - Duodenum	Additional description: Ulcer, GI - Duodenum		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Vomiting	Additional description: Vomiting		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1518	1587	1045
Hepatobiliary disorders			
Cholecystitis	Additional description: Cholecystitis		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary/Pancreas	Additional description: Hepatobiliary/Pancreas		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Skin and subcutaneous tissue disorders			
Acne	Additional description: Acne		
subjects affected / exposed	2 / 164 (1.22%)	3 / 174 (1.72%)	0 / 118 (0.00%)
occurrences (all)	2	10	0
Alopecia	Additional description: Alopecia		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1508	1565	1037
Decubitus	Additional description: Decubitus		

subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	2	0
Dermatology - other (furuncle)	Additional description: Dermatology - other (furuncle)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Dermatology - other (perineal nodule)	Additional description: Dermatology - other (perineal nodule)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Dermatology/Skin - other	Additional description: Dermatology/Skin - other		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Dermatology/Skin - other (Actinic keratosis)	Additional description: Dermatology/Skin - other (Actinic keratosis)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Dermatology/Skin - Other (blister)	Additional description: Dermatology/Skin - Other (blister)		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	1	0
Dermatology/Skin - Other (cyst)	Additional description: Dermatology/Skin - Other (cyst)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	3	0	0
Dermatology/Skin - Other (exacerbation of solar keratosis)	Additional description: Dermatology/Skin - Other (exacerbation of solar keratosis)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	3	0
Dermatology/Skin - Other (Increase in facial hair)	Additional description: Dermatology/Skin - Other (Increase in facial hair)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Dermatology/Skin - Other (Skin pigmentation)	Additional description: Dermatology/Skin - Other (Skin pigmentation)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Dry skin	Additional description: Dry skin		
subjects affected / exposed	17 / 164 (10.37%)	11 / 174 (6.32%)	5 / 118 (4.24%)
occurrences (all)	37	33	23
Hand-foot	Additional description: Hand-foot		

subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Hand-foot syndrome	Additional description: Hand-foot syndrome		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1582	1038
Hyperpigmentation	Additional description: Hyperpigmentation		
subjects affected / exposed	1 / 164 (0.61%)	4 / 174 (2.30%)	1 / 118 (0.85%)
occurrences (all)	1	9	8
Infection - Skin	Additional description: Infection - Skin		
subjects affected / exposed	9 / 164 (5.49%)	8 / 174 (4.60%)	9 / 118 (7.63%)
occurrences (all)	13	12	12
Infection - Skin (cellulitis)	Additional description: Infection - Skin (cellulitis)		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	2	4	0
Nail changes	Additional description: Nail changes		
subjects affected / exposed	5 / 164 (3.05%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	8	1	5
Pain - Anus	Additional description: Pain - Anus		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pain - Scalp	Additional description: Pain - Scalp		
subjects affected / exposed	2 / 164 (1.22%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	3	3	0
Petechiae	Additional description: Petechiae		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	8	2	0
Photosensitivity	Additional description: Photosensitivity		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Pruritus	Additional description: Pruritus		
subjects affected / exposed	16 / 164 (9.76%)	20 / 174 (11.49%)	6 / 118 (5.08%)
occurrences (all)	26	35	11
Rash	Additional description: Rash		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1539	1577	1047

Skin - Other (lump)	Additional description: Skin - Other (lump)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Skin - Other (solar keratosis)	Additional description: Skin - Other (solar keratosis)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Sweating	Additional description: Sweating		
subjects affected / exposed	6 / 164 (3.66%)	4 / 174 (2.30%)	5 / 118 (4.24%)
occurrences (all)	13	11	11
Ulceration	Additional description: Ulceration		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences (all)	1	0	12
Renal and urinary disorders			
Cystitis	Additional description: Cystitis		
subjects affected / exposed	6 / 164 (3.66%)	4 / 174 (2.30%)	2 / 118 (1.69%)
occurrences (all)	10	4	2
Haemolysis	Additional description: Haemolysis		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Hemoglobinuria	Additional description: Hemoglobinuria		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	5	0	0
Incontinence	Additional description: Incontinence		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	1	1	1
Incontinence, urinary	Additional description: Incontinence, urinary		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	4 / 118 (3.39%)
occurrences (all)	0	2	4
Obstruction, GU (renal)	Additional description: Obstruction, GU (renal)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	4	0
Pain - Bladder	Additional description: Pain - Bladder		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences (all)	2	0	7
Proteinuria	Additional description: Proteinuria		

subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1507	1570	1037
Renal - Other (dysuria)	Additional description: Renal - Other (dysuria)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Renal - Other (hematuria)	Additional description: Renal - Other (hematuria)		
subjects affected / exposed	0 / 164 (0.00%)	3 / 174 (1.72%)	0 / 118 (0.00%)
occurrences (all)	0	3	0
Renal - Other (hydronephrosis)	Additional description: Renal - Other (hydronephrosis)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Renal - Other (microscopic haematuria)	Additional description: Renal - Other (microscopic haematuria)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Renal - Other (polyuria)	Additional description: Renal - Other (polyuria)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Renal - Other (proteinuria)	Additional description: Renal - Other (proteinuria)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Renal/Genitourinary	Additional description: Renal/Genitourinary		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Urinary frequency	Additional description: Urinary frequency		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences (all)	1	7	1
Endocrine disorders			
Hyperparathyroidism	Additional description: Hyperparathyroidism		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Hyperthyroidism	Additional description: Hyperthyroidism		
subjects affected / exposed	12 / 164 (7.32%)	8 / 174 (4.60%)	1 / 118 (0.85%)
occurrences (all)	41	18	3
Hypothyroidism	Additional description: Hypothyroidism		

subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1533	1570	1040
Thyroid function	Additional description: Thyroid function		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthritis	Additional description: Arthritis		
subjects affected / exposed	3 / 164 (1.83%)	5 / 174 (2.87%)	2 / 118 (1.69%)
occurrences (all)	8	9	2
Auditory/Ear - Other (Muscle tearing in right ear)	Additional description: Auditory/Ear - Other (Muscle tearing in right ear)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Infection - Joint	Additional description: Infection - Joint		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Joint-function	Additional description: Joint-function		
subjects affected / exposed	2 / 164 (1.22%)	4 / 174 (2.30%)	1 / 118 (0.85%)
occurrences (all)	2	15	3
Joint - effusion	Additional description: Joint - effusion		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Joint function	Additional description: Joint function		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	2
Muscle weakness	Additional description: Muscle weakness		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	1	1	0
Muscle weakness - Distal	Additional description: Muscle weakness - Distal		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1507	1565	1038
Muscle weakness - Extremity-lower	Additional description: Muscle weakness - Extremity-lower		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	1 / 118 (0.85%)
occurrences (all)	0	1	2
Muscle weakness - Extremity-upper	Additional description: Muscle weakness - Extremity-upper		

subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Muscle weakness - Proximal	Additional description: Muscle weakness - Proximal		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Muscle weakness - Whole body/generalized	Additional description: Muscle weakness - Whole body/generalized		
subjects affected / exposed	6 / 164 (3.66%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	13	1	8
Musculoskeletal - other (cyst on leg)	Additional description: Musculoskeletal - other (cyst on leg)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal - Other (injury)	Additional description: Musculoskeletal - Other (injury)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Musculoskeletal - Other (plantar fascitis)	Additional description: Musculoskeletal - Other (plantar fascitis)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal - other (pulled muscle)	Additional description: Musculoskeletal - other (pulled muscle)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal - Other (tennis elbow flare)	Additional description: Musculoskeletal - Other (tennis elbow flare)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Musculoskeletal - Other (tennis elbow)	Additional description: Musculoskeletal - Other (tennis elbow)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	3
Musculoskeletal - Other (tightness - chest)	Additional description: Musculoskeletal - Other (tightness - chest)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal - Other (tightness - upper back)	Additional description: Musculoskeletal - Other (tightness - upper back)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	9

Musculoskeletal/Soft Tissue - Swelling of ankles	Additional description: Musculoskeletal/Soft Tissue - Swelling of ankles		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	1	2	0
Musculosketal - other (trigger finger)	Additional description: Musculosketal - other (trigger finger)		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	18	0	0
Myositis	Additional description: Myositis		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1506	1565	1037
Osteoporosis	Additional description: Osteoporosis		
subjects affected / exposed	2 / 164 (1.22%)	3 / 174 (1.72%)	0 / 118 (0.00%)
occurrences (all)	8	11	0
Pain - Back	Additional description: Pain - Back		
subjects affected / exposed	17 / 164 (10.37%)	13 / 174 (7.47%)	10 / 118 (8.47%)
occurrences (all)	52	30	35
Pain - Bone	Additional description: Pain - Bone		
subjects affected / exposed	4 / 164 (2.44%)	7 / 174 (4.02%)	2 / 118 (1.69%)
occurrences (all)	6	18	2
Pain - Buttock	Additional description: Pain - Buttock		
subjects affected / exposed	1 / 164 (0.61%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	1	5	0
Pain - Dental/teeth/peridontal	Additional description: Pain - Dental/teeth/peridontal		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Pain - Extremity-limb	Additional description: Pain - Extremity-limb		
subjects affected / exposed	27 / 164 (16.46%)	17 / 174 (9.77%)	18 / 118 (15.25%)
occurrences (all)	48	30	39
Pain - Hip	Additional description: Pain - Hip		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Pain - Joint	Additional description: Pain - Joint		
subjects affected / exposed	35 / 164 (21.34%)	37 / 174 (21.26%)	26 / 118 (22.03%)
occurrences (all)	90	93	110
Pain - Muscle	Additional description: Pain - Muscle		

subjects affected / exposed	20 / 164 (12.20%)	36 / 174 (20.69%)	16 / 118 (13.56%)
occurrences (all)	47	81	55
Pain - Musculoskeletal	Additional description: Pain - Musculoskeletal		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Pain - Neck	Additional description: Pain - Neck		
subjects affected / exposed	2 / 164 (1.22%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	5	0	1
Infections and infestations			
Infection	Additional description: Infection		
subjects affected / exposed	5 / 164 (3.05%)	4 / 174 (2.30%)	2 / 118 (1.69%)
occurrences (all)	5	4	2
Infection - Abdomen	Additional description: Infection - Abdomen		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Infection - Abdomen NOS	Additional description: Infection - Abdomen NOS		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Infection - Bladder (urinary)	Additional description: Infection - Bladder (urinary)		
subjects affected / exposed	5 / 164 (3.05%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	5	3	1
Infection - Bronchus	Additional description: Infection - Bronchus		
subjects affected / exposed	11 / 164 (6.71%)	19 / 174 (10.92%)	13 / 118 (11.02%)
occurrences (all)	14	25	20
Infection - Catheter-related	Additional description: Infection - Catheter-related		
subjects affected / exposed	3 / 164 (1.83%)	3 / 174 (1.72%)	0 / 118 (0.00%)
occurrences (all)	3	3	0
Infection - Conjunctiva	Additional description: Infection - Conjunctiva		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	2 / 118 (1.69%)
occurrences (all)	2	1	2
Infection - Dental-tooth	Additional description: Infection - Dental-tooth		
subjects affected / exposed	2 / 164 (1.22%)	3 / 174 (1.72%)	0 / 118 (0.00%)
occurrences (all)	2	3	0
Infection - Ear	Additional description: Infection - Ear		
subjects affected / exposed	3 / 164 (1.83%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	6	0	0

Infection - Eye NOS	Additional description: Infection - Eye NOS		
subjects affected / exposed	0 / 164 (0.00%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	0	3	1
Infection - Gallbladder (cholecystitis)	Additional description: Infection - Gallbladder (cholecystitis)		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Infection - Gastrointestinal - Abdomen NOS	Additional description: Infection - Gastrointestinal - Abdomen NOS		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Infection - Inner ear	Additional description: Infection - Inner ear		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Infection - Kidney	Additional description: Infection - Kidney		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Infection - Larynx	Additional description: Infection - Larynx		
subjects affected / exposed	3 / 164 (1.83%)	1 / 174 (0.57%)	5 / 118 (4.24%)
occurrences (all)	3	1	5
Infection - Lung	Additional description: Infection - Lung		
subjects affected / exposed	2 / 164 (1.22%)	4 / 174 (2.30%)	1 / 118 (0.85%)
occurrences (all)	2	4	1
Infection - Middle ear	Additional description: Infection - Middle ear		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Infection - Nose	Additional description: Infection - Nose		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Infection - Oral cavity	Additional description: Infection - Oral cavity		
subjects affected / exposed	0 / 164 (0.00%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	0	2	0
Infection - Oral cavity-gums	Additional description: Infection - Oral cavity-gums		
subjects affected / exposed	8 / 164 (4.88%)	4 / 174 (2.30%)	2 / 118 (1.69%)
occurrences (all)	9	4	2
Infection - Other (herpes simplex)	Additional description: Infection - Other (herpes simplex)		

subjects affected / exposed	3 / 164 (1.83%)	5 / 174 (2.87%)	1 / 118 (0.85%)
occurrences (all)	4	8	3
Infection - Other (shingles)	Additional description: Infection - Other (shingles)		
subjects affected / exposed	2 / 164 (1.22%)	3 / 174 (1.72%)	1 / 118 (0.85%)
occurrences (all)	2	5	1
Infection - Other abscess	Additional description: Infection - Other abscess		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Infection - other catheter-related	Additional description: Infection - other catheter-related		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Infection - Perianal	Additional description: Infection - Perianal		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Infection - Peritoneal cavity	Additional description: Infection - Peritoneal cavity		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Infection - Sinus	Additional description: Infection - Sinus		
subjects affected / exposed	4 / 164 (2.44%)	4 / 174 (2.30%)	4 / 118 (3.39%)
occurrences (all)	8	5	6
Infection - Soft tissue	Additional description: Infection - Soft tissue		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Infection - Soft tissue NOS	Additional description: Infection - Soft tissue NOS		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	2	0	0
Infection - Ungual (nails)	Additional description: Infection - Ungual (nails)		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Infection - Upper Airway NOS	Additional description: Infection - Upper Airway NOS		
subjects affected / exposed	31 / 164 (18.90%)	30 / 174 (17.24%)	18 / 118 (15.25%)
occurrences (all)	49	38	22
Infection - Upper respiratory	Additional description: Infection - Upper respiratory		
subjects affected / exposed	4 / 164 (2.44%)	4 / 174 (2.30%)	2 / 118 (1.69%)
occurrences (all)	4	4	2
Infection - Urinary tract NOS	Additional description: Infection - Urinary tract NOS		

subjects affected / exposed	23 / 164 (14.02%)	31 / 174 (17.82%)	14 / 118 (11.86%)
occurrences (all)	35	56	31
Infection - Vagina	Additional description: Infection - Vagina		
subjects affected / exposed	5 / 164 (3.05%)	2 / 174 (1.15%)	2 / 118 (1.69%)
occurrences (all)	5	2	2
Infection - Vulva	Additional description: Infection - Vulva		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences (all)	0	0	3
Infection with Grade 3 or 4 ANC	Additional description: Infection with Grade 3 or 4 ANC		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1525	1583	1047
Bicarbonate, serum-low	Additional description: Bicarbonate, serum-low		
subjects affected / exposed	1 / 164 (0.61%)	0 / 174 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Dehydration	Additional description: Dehydration		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1509	1573	1038
Diabetes	Additional description: Diabetes		
subjects affected / exposed	1 / 164 (0.61%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	6	2	0
Hypercalcemia	Additional description: Hypercalcemia		
subjects affected / exposed	3 / 164 (1.83%)	10 / 174 (5.75%)	3 / 118 (2.54%)
occurrences (all)	3	12	13
Hyperglycemia	Additional description: Hyperglycemia		
subjects affected / exposed	8 / 164 (4.88%)	9 / 174 (5.17%)	6 / 118 (5.08%)
occurrences (all)	13	14	11
Hyperkalemia	Additional description: Hyperkalemia		
subjects affected / exposed	1 / 164 (0.61%)	4 / 174 (2.30%)	2 / 118 (1.69%)
occurrences (all)	2	9	4
Hypernatremia	Additional description: Hypernatremia		

subjects affected / exposed	3 / 164 (1.83%)	2 / 174 (1.15%)	0 / 118 (0.00%)
occurrences (all)	3	2	0
Hypertriglyceridemia	Additional description: Hypertriglyceridemia		
subjects affected / exposed	0 / 164 (0.00%)	0 / 174 (0.00%)	2 / 118 (1.69%)
occurrences (all)	0	0	11
Hyperuricemia	Additional description: Hyperuricemia		
subjects affected / exposed	1 / 164 (0.61%)	5 / 174 (2.87%)	3 / 118 (2.54%)
occurrences (all)	1	11	7
Hypoalbuminemia	Additional description: Hypoalbuminemia		
subjects affected / exposed	13 / 164 (7.93%)	10 / 174 (5.75%)	8 / 118 (6.78%)
occurrences (all)	21	22	15
Hypocalcemia	Additional description: Hypocalcemia		
subjects affected / exposed	17 / 164 (10.37%)	21 / 174 (12.07%)	3 / 118 (2.54%)
occurrences (all)	37	38	4
Hypoglycemia	Additional description: Hypoglycemia		
subjects affected / exposed	4 / 164 (2.44%)	2 / 174 (1.15%)	1 / 118 (0.85%)
occurrences (all)	6	4	1
Hypokalemia	Additional description: Hypokalemia		
subjects affected / exposed	164 / 164 (100.00%)	174 / 174 (100.00%)	116 / 118 (98.31%)
occurrences (all)	1510	1570	1040
Hypomagnesemia	Additional description: Hypomagnesemia		
subjects affected / exposed	63 / 164 (38.41%)	63 / 174 (36.21%)	31 / 118 (26.27%)
occurrences (all)	244	299	123
Hyponatremia	Additional description: Hyponatremia		
subjects affected / exposed	16 / 164 (9.76%)	16 / 174 (9.20%)	8 / 118 (6.78%)
occurrences (all)	30	30	22
Hypophosphatemia	Additional description: Hypophosphatemia		
subjects affected / exposed	13 / 164 (7.93%)	5 / 174 (2.87%)	10 / 118 (8.47%)
occurrences (all)	16	8	14
Obesity	Additional description: Obesity		
subjects affected / exposed	0 / 164 (0.00%)	1 / 174 (0.57%)	0 / 118 (0.00%)
occurrences (all)	0	2	0

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? Yes

Date	Interruption	Restart date
03 October 2011	ICON6 was an academic trial with a planned sample size of 2000 that opened to recruitment in December 2007. In October 2011, the Pharma partner (AstraZeneca) made the decision to terminate development of cediranib and discontinued manufacture of the agent. The resultant loss of drug supply led to recruitment being discontinued in December 2011, at which point 486 women had been randomised amongst the three arms.	-

Notes:

Limitations and caveats

None reported