



Clinical trial results:

A randomized phase 2 study comparing different dose-approaches of induction treatment (first cycle) of regorafenib in metastatic colorectal cancer (mCRC) patients

Summary

EudraCT number	2016-000640-34
Trial protocol	ES FR IT
Global end of trial date	24 September 2018

Results information

Result version number	v1 (current)
This version publication date	01 May 2020
First version publication date	01 May 2020

Trial information

Trial identification

Sponsor protocol code	TTD-16-01
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	TTD
Sponsor organisation address	Téllez 30, Madrid, Spain, 28007
Public contact	Inmaculada Ruiz de Mena, Grupo de Tratamiento de los Tumores Digestivos (TTD), +34 91378 82 75, ttd@ttdgroup.org
Scientific contact	Inmaculada Ruiz de Mena, Grupo de Tratamiento de los Tumores Digestivos (TTD), +34 91378 82 75, ttd@ttdgroup.org

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	13 February 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the safety and tolerability of different dose-escalation approaches of regorafenib in mCRC patients.

Protection of trial subjects:

Any medication that patients needed for their correct clinical control (except prohibited therapies), according to investigator's criteria were allowed.

Background therapy:

Standard therapies for concurrent medical conditions. Prophylactic anti-emetics could be administered according to standard practice. Treatment with non-conventional therapies (eg, herbs or acupuncture) or vitamin/mineral supplements was acceptable provided that such agents did not interfere, in the opinion of the investigator, with the study endpoints. Bisphosphonates. Subjects taking narrow therapeutic index medications, such as warfarin, quinidine, cyclosporine, and digoxin, were monitored proactively. Contrast agents used in CT or MRI. G-CSF and other hematopoietic growth factors could be used during the study for the management of acute toxicity such as febrile neutropenia when clinically indicated or at the discretion of the investigator; however, there could not be substituted for a required dose reduction. Long-term administration of erythropoietin was permitted.

Evidence for comparator: -

Actual start date of recruitment	01 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 277
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	299
EEA total number of subjects	299

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)	159
From 65 to 84 years	140
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	299
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Number of subjects completed	299
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Period 1

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

Are arms mutually exclusive?	Yes
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Arm title	Arm A
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Arm description:

Control arm: 160 mg regorafenib/day 3 weeks every 4 weeks

Arm type	Control
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Investigational medicinal product name	Regorafenib
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Buccal tablet
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Routes of administration	Oral use
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Dosage and administration details:

Regorafenib 160 mg/day 3weeks / 4 weeks

Arm title	Arm B
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Arm description:

120 mg/day 3 weeks every 4 weeks (first cycle), 160 mg/day 3 weeks/4 weeks if no limiting toxicities

Arm type	Experimental
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Investigational medicinal product name	Regorafenib
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Tablet
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Routes of administration	Oral use
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Dosage and administration details:

120 mg/day 3 weeks every 4 weeks 1st cycle, 160 mg/day 3 weeks every 4 weeks if no limiting toxicities

Arm title	Arm C
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Arm description:

160 mg/day 1 week on, 1 week off during the first cycle, Dose escalation to the standard dose of 160 mg (4 tablets of 40 mg)

taken once daily for 3 weeks followed by 1 week off therapy from cycle 2 onwards if no limiting toxicities

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

Dosage and administration details:

160 mg/day, 1 week on/1 week off 1st cycle: 160 mg/day 3 weeks on/1week off 2nd cycle on

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	101	99	99
Completed	100	98	99
Not completed	1	1	0
Physician decision	1	-	-
Adverse event, non-fatal	-	1	-

Baseline characteristics

Reporting groups

Reporting group title	Arm A
Reporting group description:	
Control arm: 160 mg regorafenib/day 3 weeks every 4 weeks	
Reporting group title	Arm B
Reporting group description:	
120 mg/day 3 weeks every 4 weeks (first cycle), 160 mg/day 3 weeks/4 weeks if no limiting toxicities	
Reporting group title	Arm C
Reporting group description:	
160 mg/day 1 week on, 1 week off during the first cycle, Dose escalation to the standard dose of 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy from cycle 2 onwards if no limiting toxicities	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	101	99	99
Age categorical			
Units: Subjects			
Adults (18-64 years)	50	56	53
From 65-84 years	51	43	46
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	63.2	62.34	62.56
standard deviation	± 9.08	± 9.86	± 9.92
Gender categorical			
Units: Subjects			
Female	42	46	47
Male	59	53	52
ECOG			
Units: Subjects			
ECOG 0	36	33	35
ECOG 1	65	66	64
Cancer history-Location			
Units: Subjects			
Rectum	31	22	39
Colon	53	59	49
Colon and rectum	17	18	11
Histology			
Units: Subjects			
Adenocarcinoma	89	90	91
Missing	6	5	7
Carcinoma not otherwise specified	0	1	0
Mucinous carcinoma	3	0	0
UK	3	2	1
ND	0	1	0
Histological Grade			
Units: Subjects			

G1: Well-differentiated	15	16	21
G2: Moderately differentiated	31	30	38
G3: Poorly differentiated	10	7	5
Gx: Grade cannot assessed	4	3	4
Missing	1	0	0
Unknown	40	43	31
Previous radiotherapy			
Units: Subjects			
YES	28	22	27
NO	73	77	72
Number of prior treatment lines			
Units: Treatment lines			
arithmetic mean	4.12	4.21	3.85
standard deviation	± 1.81	± 4.00	± 3.00

Reporting group values	Total		
Number of subjects	299		
Age categorical			
Units: Subjects			
Adults (18-64 years)	159		
From 65-84 years	140		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	135		
Male	164		
ECOG			
Units: Subjects			
ECOG 0	104		
ECOG 1	195		
Cancer history-Location			
Units: Subjects			
Rectum	92		
Colon	161		
Colon and rectum	46		
Histology			
Units: Subjects			
Adenocarcinoma	270		
Missing	18		
Carcinoma not otherwise specified	1		
Mucinous carcinoma	3		
UK	6		
ND	1		
Histological Grade			
Units: Subjects			
G1: Well-differentiated	52		
G2: Moderately differentiated	99		

G3: Poorly differentiated	22		
Gx: Grade cannot assessed	11		
Missing	1		
Unknown	114		
Previous radiotherapy			
Units: Subjects			
YES	77		
NO	222		
Number of prior treatment lines			
Units: Treatment lines			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
Control arm: 160 mg regorafenib/day 3 weeks every 4 weeks	
Reporting group title	Arm B
Reporting group description:	
120 mg/day 3 weeks every 4 weeks (first cycle), 160 mg/day 3 weeks/4 weeks if no limiting toxicities	
Reporting group title	Arm C
Reporting group description:	
160 mg/day 1 week on, 1 week off during the first cycle, Dose escalation to the standard dose of 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy from cycle 2 onwards if no limiting toxicities	

Primary: • Percentage of patients with G3/G4 treatment-related AEs in each arm according to CTCAE v4.03 criteria.

End point title	• Percentage of patients with G3/G4 treatment-related AEs in each arm according to CTCAE v4.03 criteria.
End point description:	
End point type	Primary
End point timeframe:	
Overall study	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	98	99	
Units: percentage	60	55	54	

Statistical analyses

Statistical analysis title	% of pt with G3/G4 treat-rel AEs in each arm
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7262
Method	Chi-squared
Parameter estimate	Risk difference (RD)

Secondary: Percentage of total administrated dose over the planned dose received

End point title	Percentage of total administrated dose over the planned dose received
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End point description:

End point type	Secondary
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End point timeframe:

Overall study

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	98	99	
Units: dosage form				
arithmetic mean (standard deviation)	82.25 ($\pm$ 29.51)	67.30 ($\pm$ 26.93)	71.81 ($\pm$ 25.14)	

Statistical analyses

Statistical analysis title	% of total adm dose over the plan dose received
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0217
Method	Kruskal-wallis

Secondary: Dose intensity during the whole treatment

End point title	Dose intensity during the whole treatment
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End point description:

End point type	Secondary
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End point timeframe:

Overall trial

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	98	99	
Units: dosage form				
arithmetic mean (standard deviation)	68.54 ($\pm$ 24.60)	66.42 ($\pm$ 24.83)	74.92 ($\pm$ 23.65)	

Statistical analyses

Statistical analysis title	Dose intensity dur whole treatment
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.0002
Method	Kruskal-wallis

Secondary: Percentage of dose reductions in each arm.

End point title	Percentage of dose reductions in each arm.
End point description:	
End point type	Secondary
End point timeframe:	
Overall trial	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	98	99	
Units: Percentage	39	38	25	

Statistical analyses

Statistical analysis title	% of dose red in each arm
Comparison groups	Arm B v Arm C v Arm A
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Odds ratio (OR)
Point estimate	34.3434
Confidence interval	
level	95 %
sides	2-sided
lower limit	28.9549
upper limit	40.0479

Secondary: Percentage of dose delays in each arm

End point title	Percentage of dose delays in each arm
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End point description:

End point type	Secondary
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End point timeframe:

Overall study

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	98	99	
Units: Percentage	35	33	29	

Statistical analyses

Statistical analysis title	Percentage of dose delays in each arm
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Comparison groups	Arm A v Arm B v Arm C
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Number of subjects included in analysis	297
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Analysis specification	Pre-specified
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Analysis type	equivalence
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Parameter estimate	Odds ratio (OR)
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Point estimate	32.6599
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	27.3549
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upper limit	38.3151
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Secondary: Dose intensity during the first two cycles

End point title	Dose intensity during the first two cycles
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End point description:

End point type	Secondary
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End point timeframe:

Overall trial

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	98	99	
Units: dosage form				
arithmetic mean (standard deviation)	90.77 (± 27.91)	77.09 (± 24.94)	79.99 (± 22.41)	

Statistical analyses

Statistical analysis title	Dose intensity during the first 2 cycles
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.001
Method	Kruskal-wallis

Secondary: Disease control rate

End point title	Disease control rate
End point description:	
Number of patients with complete response, partial response or stable disease	
End point type	Secondary
End point timeframe:	
Overall study	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	99	99	
Units: Subjects				
Complete response	0	0	0	
Partial response	2	2	3	
Stable disease	31	34	32	

Statistical analyses

Statistical analysis title	Disease control rate
Comparison groups	Arm A v Arm B v Arm C

Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.8515
Method	Chi-squared

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)
End point description: Time from randomization until the date of the first disease progression, observed radiologically, or death (whichever comes first). Subjects who have shown no progression while in the study and who did not die in the study were censored at the date of their last evaluable disease assessment.	
End point type	Secondary
End point timeframe:	
Overall trial	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	99	99	
Units: months				
median (confidence interval 95%)	1.94 (1.84 to 2.07)	2 (1.87 to 2.86)	1.97 (1.87 to 2.2)	

Statistical analyses

Statistical analysis title	Progression free survival
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.3795
Method	Logrank

Secondary: Time to treatment failure (TTF)

End point title	Time to treatment failure (TTF)
End point description: Time from randomization until the date the decision is made to end the treatment period, for any reason. For subjects who remained in the treatment period at the time of the analysis, time to treatment failure was censored at the date of their last evaluable disease assessment.	
End point type	Secondary
End point timeframe:	
Overall trial	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	99	99	
Units: months				
median (confidence interval 95%)	1.87 (1.81 to 2.04)	1.94 (1.84 to 2.07)	1.94 (1.84 to 2.14)	

Statistical analyses

Statistical analysis title	Time to treatment failure
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.2114
Method	Logrank
Parameter estimate	Logrank

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	Time from randomization until the date of death due to any cause. Subjects who were lost to follow-up or who did not die by the end of the study were censored at the last contact date.
End point type	Secondary
End point timeframe:	
Overall trial	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	101	99	99	
Units: months				
median (confidence interval 95%)	7.39 (5.98 to 9.34)	8.58 (5.78 to 10.13)	7.13 (5.85 to 8.22)	

Statistical analyses

Statistical analysis title	Overall survival
Comparison groups	Arm A v Arm B v Arm C

Number of subjects included in analysis	299
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.7222
Method	Logrank
Parameter estimate	Logrank

Secondary: Proportion of patients who complete 2 cycles and who intend to initiate cycle 3

End point title	Proportion of patients who complete 2 cycles and who intend to initiate cycle 3
End point description: Proportion of patients in each arm who completed 2 cycles of treatment and who intended to initiate cycle 3 if no progression was noted on the planned 8-week scan.	
End point type	Secondary
End point timeframe: Overall trial	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	98	99	
Units: Percentage	39	43	45	

Statistical analyses

Statistical analysis title	Prop of pt who complet 2 cyc
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	297
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.6309
Method	Chi-squared
Parameter estimate	Risk difference (RD)

Secondary: Proportion of patients who stopped the trial due to disease progression at planned 8-week scan

End point title	Proportion of patients who stopped the trial due to disease progression at planned 8-week scan
End point description: Proportion of patients who stopped the trial due to disease progression in each arm at the planned 8-week scan	
End point type	Secondary

End point timeframe:

Overall trial

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	61	55	54	
Units: Percentage	63	63	61	

Statistical analyses

Statistical analysis title	Prop pt who stop trial at 8-week scan
Comparison groups	Arm A v Arm B v Arm C
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.9442
Method	Chi-squared
Parameter estimate	Risk difference (RD)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall trial

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Arm A
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Reporting group description: -

Reporting group title	Arm B
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Reporting group description: -

Reporting group title	Arm C
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Reporting group description: -

Serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 100 (29.00%)	29 / 98 (29.59%)	24 / 99 (24.24%)
number of deaths (all causes)	80	78	83
number of deaths resulting from adverse events	6	6	8
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 100 (1.00%)	1 / 98 (1.02%)	4 / 99 (4.04%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
pyrexia			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			

subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	2 / 99 (2.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Performance status decreased			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General physical health deterioration			
subjects affected / exposed	1 / 100 (1.00%)	1 / 98 (1.02%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Pain			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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
Sudden death			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Malaise			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	2 / 99 (2.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	1 / 100 (1.00%)	1 / 98 (1.02%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (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
Investigations			
blood glycaemia decreased			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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			
Overdose			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	2 / 99 (2.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Acute coronary syndrome			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (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
Congestive cardiomyopathy			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Atrial fibrillation			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Leukoencephalopathy			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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
Seizure			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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			
Febrile neutropenia			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Iridocyclitis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
subjects affected / exposed	0 / 100 (0.00%)	2 / 98 (2.04%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proctalgia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal perforation			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterovesical fistula			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine perforation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 100 (2.00%)	1 / 98 (1.02%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intestinal perforation			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (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
Enteritis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (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
Faecaloma			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 100 (0.00%)	3 / 98 (3.06%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	2 / 3	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 2	1 / 1
Jaundice cholestatic			
subjects affected / exposed	2 / 100 (2.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic pain			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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
Cholecystitis acute			

subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (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
Bile duct obstruction			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 100 (0.00%)	2 / 98 (2.04%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic skin eruption			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ulcer			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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
Rash			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
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			
Urinary tract obstruction			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
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			
Back pain			
subjects affected / exposed	2 / 100 (2.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 100 (5.00%)	2 / 98 (2.04%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	2 / 99 (2.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Enterocolitis infectious			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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
Sepsis			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abdominal sepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Urosepsis			
subjects affected / exposed	1 / 100 (1.00%)	0 / 98 (0.00%)	0 / 99 (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
Anal abscess			
subjects affected / exposed	0 / 100 (0.00%)	0 / 98 (0.00%)	1 / 99 (1.01%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Abscess			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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
Urinary tract infection			
subjects affected / exposed	0 / 100 (0.00%)	1 / 98 (1.02%)	0 / 99 (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

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

Non-serious adverse events	Arm A	Arm B	Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	100 / 100 (100.00%)	98 / 98 (100.00%)	99 / 99 (100.00%)
Investigations			
Blood potassium decreased			
subjects affected / exposed	24 / 100 (24.00%)	20 / 98 (20.41%)	25 / 99 (25.25%)
occurrences (all)	24	20	25
Hyperbilirubinaemia			
subjects affected / exposed	20 / 100 (20.00%)	25 / 98 (25.51%)	19 / 99 (19.19%)
occurrences (all)	20	25	19
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	12 / 100 (12.00%) 12	20 / 98 (20.41%) 20	10 / 99 (10.10%) 10
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6	15 / 98 (15.31%) 15	8 / 99 (8.08%) 8
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 7	13 / 98 (13.27%) 13	8 / 99 (8.08%) 8
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	5 / 100 (5.00%) 5	9 / 98 (9.18%) 9	5 / 99 (5.05%) 5
Amylase increased subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6	6 / 98 (6.12%) 6	6 / 99 (6.06%) 6
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	46 / 100 (46.00%) 46	41 / 98 (41.84%) 41	48 / 99 (48.48%) 48
Nervous system disorders Headache subjects affected / exposed occurrences (all)	11 / 100 (11.00%) 11	4 / 98 (4.08%) 4	13 / 99 (13.13%) 13
Aphonia subjects affected / exposed occurrences (all)	8 / 100 (8.00%) 8	11 / 98 (11.22%) 11	3 / 99 (3.03%) 3
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all)	22 / 100 (22.00%) 22	14 / 98 (14.29%) 14	14 / 99 (14.14%) 14
Anaemia subjects affected / exposed occurrences (all)	13 / 100 (13.00%) 13	9 / 98 (9.18%) 9	19 / 99 (19.19%) 19
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	67 / 100 (67.00%) 67	63 / 98 (64.29%) 63	68 / 99 (68.69%) 68

Mucosal inflammation subjects affected / exposed occurrences (all)	25 / 100 (25.00%) 25	22 / 98 (22.45%) 22	23 / 99 (23.23%) 23
pyrexia subjects affected / exposed occurrences (all)	24 / 100 (24.00%) 24	20 / 98 (20.41%) 20	16 / 99 (16.16%) 16
Fatigue subjects affected / exposed occurrences (all)	11 / 100 (11.00%) 11	11 / 98 (11.22%) 11	15 / 99 (15.15%) 15
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	47 / 100 (47.00%) 47	34 / 98 (34.69%) 34	41 / 99 (41.41%) 41
Abdominal pain subjects affected / exposed occurrences (all)	22 / 100 (22.00%) 22	20 / 98 (20.41%) 20	17 / 99 (17.17%) 17
Constipation subjects affected / exposed occurrences (all)	18 / 100 (18.00%) 18	17 / 98 (17.35%) 17	18 / 99 (18.18%) 18
Nausea subjects affected / exposed occurrences (all)	17 / 100 (17.00%) 17	14 / 98 (14.29%) 14	19 / 99 (19.19%) 19
Vomiting subjects affected / exposed occurrences (all)	13 / 100 (13.00%) 13	16 / 98 (16.33%) 16	14 / 99 (14.14%) 14
Abdominal pain upper subjects affected / exposed occurrences (all)	12 / 100 (12.00%) 12	13 / 98 (13.27%) 13	6 / 99 (6.06%) 6
Dry mouth subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 7	6 / 98 (6.12%) 6	4 / 99 (4.04%) 4
Stomatitis subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6	4 / 98 (4.08%) 4	6 / 99 (6.06%) 6
Respiratory, thoracic and mediastinal disorders			

Dysphonia subjects affected / exposed occurrences (all)	51 / 100 (51.00%) 51	43 / 98 (43.88%) 43	44 / 99 (44.44%) 44
Cough subjects affected / exposed occurrences (all)	9 / 100 (9.00%) 9	12 / 98 (12.24%) 12	4 / 99 (4.04%) 4
Dyspnoea subjects affected / exposed occurrences (all)	7 / 100 (7.00%) 7	4 / 98 (4.08%) 4	7 / 99 (7.07%) 7
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysesthesia syndrome subjects affected / exposed occurrences (all)	40 / 100 (40.00%) 40	52 / 98 (53.06%) 52	41 / 99 (41.41%) 41
Rash subjects affected / exposed occurrences (all)	19 / 100 (19.00%) 19	13 / 98 (13.27%) 13	15 / 99 (15.15%) 15
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	10 / 100 (10.00%) 10	10 / 98 (10.20%) 10	9 / 99 (9.09%) 9
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	16 / 100 (16.00%) 16	15 / 98 (15.31%) 15	12 / 99 (12.12%) 12
Musculoskeletal pain subjects affected / exposed occurrences (all)	10 / 100 (10.00%) 10	6 / 98 (6.12%) 6	8 / 99 (8.08%) 8
Myalgia subjects affected / exposed occurrences (all)	6 / 100 (6.00%) 6	6 / 98 (6.12%) 6	11 / 99 (11.11%) 11
Arthralgia subjects affected / exposed occurrences (all)	4 / 100 (4.00%) 4	5 / 98 (5.10%) 5	9 / 99 (9.09%) 9
Infections and infestations Urinary tract infection			

subjects affected / exposed occurrences (all)	11 / 100 (11.00%) 11	9 / 98 (9.18%) 9	4 / 99 (4.04%) 4
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	45 / 100 (45.00%) 45	47 / 98 (47.96%) 47	37 / 99 (37.37%) 37

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2018	The substantial amendment was done in order to update the analysis section. The following changes were made from Protocol v1.0 (15-Feb-2016) to protocol v2.0 (9-Jul-18).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported