EU Clinical Trials Register

Clinical trial results:
A Phase II trial to assess FOLFIRI + aflibercept efficacy in patients with oxaliplatin-pretreated metastatic colorectal cancer with or without ACE polymorphisms

Summary

EudraCT number	2016-001508-45
Trial protocol	ES
Global end of trial date	11 December 2018

Results information

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

Trial information

Trial identification

Sponsor protocol code	TTD-16-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02970916
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Grupo de Tratamiento de los Tumores Digestivos (TTD)
Sponsor organisation address	C/ Téllez Nº 30 posterior 1º oficina 4.2, Madrid, Spain, 28007
Public contact	TTD, Grupo de Tratamiento de los Tumores Digestivos (TTD), 0034 91 378 82 75, ttd@ttdgroup.org
Scientific contact	TTD, Grupo de Tratamiento de los Tumores Digestivos (TTD), 0034 91 378 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	04 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 December 2018
Global end of trial reached?	Yes
Global end of trial date	11 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess FOLFIRI + aflibercept efficacy in patients with or without angiotensin converting enzyme (ACE) polymorphisms in terms of progression-free survival (PFS).

Protection of trial subjects:

All patients included in the clinical trial received the combination of aflibercept + FOLFIRI regimen in 2-week cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal (investigator or patient decision, death, appearance of any of the exclusion criteria clinically relevant, significant non-compliance with protocol, development of a second cancer, addition of an anti-neoplastic drug other tan study drugs or pregnancy).
All patients that discontinued the study treatment were followed up every 3 months to document progression (If patients withdraw from the treatment before progression), treatment-related adverse events (AE), further cancer treatments and survival, except for those who withdrew their informed consent, were lost to follow-up or died.

Background therapy:

Not applicable

Evidence for comparator: -

Actual start date of recruitment	23 November 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 101
Worldwide total number of subjects	101
EEA total number of subjects	101

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	57
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One hundred and fifteen patients were recruited, 14 of whom were considered screening failures (noncompliance with selection criteria, n=11; withdrawal of consent n=2 and not possible to evaluate RECIST criteria due to patient`s weight, n=1). Therefore, 101 patients were finally included in this national study conducted in 15 Spanish hospitals.

Pre-assignment

Screening details:

Patients aged ≥18 years, with histologically proven colorectal adenocarcinoma, metastatic disease and ≥1 measurable unidimensional lesion using CT or MRI according to RECIST criteria. The mCRC had to be resistant to or progressive on an oxaliplatin-containing regimen. WHO performance status 0-2 and adequate bone marrow, renal and liver functions.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

Arm title	Aflibercept + FOLFIRI

Arm description:

All patients included in the clinical trial received the combination of aflibercept + FOLFIRI regimen in 2-week cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal (investigator or patient decision, death, appearance of any of the exclusion criteria clinically relevant, significant non-compliance with protocol, development of a second cancer, addition of an anti-neoplastic drug other tan study drugs or pregnancy).

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Aflibercept was administered at a dose of 4 mg/kg by intravenous infusion on day 1 of each 2-week cycle.

Investigational medicinal product name	FOLFIRI
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

FOLFIRI regimen was administered immediately after aflibercept:
Irinotecan: was administered at a dose of 180 mg/m2
Folinic acid: was administered at a dose of 400 mg/m2 (400 mg/m2 [racemic] or 200 mg/m2 [L-form]) by i.v. infusion followed by
5-Fluorouracil (5-FU) bolus: was administered at a dose of 400 mg/m2 as a bolus followed by
5-FU infusion: was administered at a dose of 2400 mg/m2 over 46 hours by continuous i.v. infusion.

Number of subjects in period 1	Aflibercept + FOLFIRI
Started	101
Completed	101

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	101	101	
Age categorical			
Units: Subjects			
Adults (18-64 years)	57	57	
From 65-84 years	44	44	
Age continuous			
Units: years			
median	63.8		
inter-quartile range (Q1-Q3)	57.7 to 71.3	-	
Gender categorical			
Units: Subjects			
Female	41	41	
Male	60	60	
ACE polymorphisms			
The genotype frequencies of the ACE polymorphisms.			
Units: Subjects			
IN/DEL	47	47	
IN/IN	14	14	
DEL/DEL	40	40	
AGTR1 polymorphisms			
The genotype frequencies of the AGTR1 polymorphisms.			
Units: Subjects			
A/A	54	54	
A/C	38	38	
C/C	9	9	
RAS status			
Units: Subjects			
Mutant	60	60	
Wild-type	34	34	
Unknown	7	7	
ACE serum levels			
Units: ng/ml			
median	161.2		
inter-quartile range (Q1-Q3)	82.5 to 320.6	-	
VEGF-A serum levels			
Units: ng/ml			
median	1.6		
inter-quartile range (Q1-Q3)	0.3 to 15.8	-	

End points

End points reporting groups

Reporting group title	Aflibercept + FOLFIRI

Reporting group description:

All patients included in the clinical trial received the combination of aflibercept + FOLFIRI regimen in 2-week cycles. Treatment was given until disease progression, unacceptable toxicity or patient withdrawal (investigator or patient decision, death, appearance of any of the exclusion criteria clinically relevant, significant non-compliance with protocol, development of a second cancer, addition of an anti-neoplastic drug other tan study drugs or pregnancy).

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Intention to treat (ITT) population: included all patients receiving at least one dose of study treatment and with quality DNA sample available for biomarker determination (N=101).

Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

Per protocol (PP) population: included all patients who met all the inclusion criteria and none of the exclusion criteria who received the study treatment as per the protocol, had at least one assessment of efficacy and/or safety post-baseline and without major protocol deviations that entailed patient's withdrawal from the study (N=89).

Subject analysis set title	IN/DEL
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ACE polymorphism IN/DEL

Subject analysis set title	IN/IN
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ACE polymorphism IN/IN

Subject analysis set title	DEL/DEL
Subject analysis set type	Sub-group analysis

Subject analysis set description:

ACE polymorphism DEL/DEL

Subject analysis set title	<1.941 ng/ml
Subject analysis set type	Sub-group analysis

Subject analysis set description:

VEFG-A levels <1.941 ng/ml

Subject analysis set title	≥1.941 ng/ml
Subject analysis set type	Sub-group analysis

Subject analysis set description:

VEFG-A levels ≥1.941 ng/ml

Primary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)[1]

End point description:

The primary study endpoint was PFS, defined as the time from inclusion to disease progression (observed radiologically) or death from any cause.

End point type	Primary

End point timeframe:

From inclusion to disease progression or death from any cause.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Absolute and relative frequency distributions were presented for qualitative variables, as well as measures of central tendency and dispersion for quantitative variables. The Kaplan–Meier method was used to analyse the primary and secondary time-to-event endpoints.

End point values	ITT	PP		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	101	89		
Units: months				
median (confidence interval 95%)	7.5 (6.0 to 8.9)	8.4 (6.9 to 9.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall surival (OS)

End point title	Overall surival (OS)

End point description:

OS was defined as time from inclusion to death from any cause

End point type	Secondary

End point timeframe:

From inclusion to death from any cause.

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	101			
Units: months				
median (confidence interval 95%)	12.6 (8.4 to 16.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression (TTP)

End point title	Time to progression (TTP)

End point description:

Time from inclusion to disease progression or death for progression

End point type	Secondary

End point timeframe:

From inclusion to disease progression or death for progression

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	101			
Units: months				
median (confidence interval 95%)	8.3 (7.1 to 9.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to treatment failure (TTF)

End point title	Time to treatment failure (TTF)
End point description:	
Time from inclusion to treatment discontinuation for any reason.	
End point type	Secondary
End point timeframe:	
From inclusion to treatment discontinuation.	

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	101			
Units: months				
median (confidence interval 95%)	6.1 (4.8 to 7.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR)

End point title	Overall response rate (ORR)
End point description:	
Percentage of patients with either a complete response (CR) or partial response (PR) according to RECIST criteria (version 1.1).	
End point type	Secondary
End point timeframe:	
From the beginning until the end of the study.	

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	101[2]			
Units: Percentage of patients				
number (confidence interval 95%)	15.8 (9.6 to 24.8)			

Notes:

[2] - PR was reported in 15.8% (n=16).

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR)

End point title	Disease control rate (DCR)

End point description:

Percentage of patients with either a complete response (CR), partial response (PR) or stable disease (SD) according to RECIST criteria (version 1.1).

End point type	Secondary

End point timeframe:

From the beginning until the end of the study.

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	101[3]			
Units: Percentage of patients				
median (confidence interval 95%)	69.3 (59.2 to 77.9)			

Notes:

[3] - PR and SD were reported in 15.8% (n=16) and 53.5% (n=54) respectively.

Statistical analyses

No statistical analyses for this end point

Secondary: ORR according to ACE polymorphisms

End point title	ORR according to ACE polymorphisms

End point description:

Percentage of patients with either a complete response (CR) or partial response (PR) according to RECIST criteria (version 1.1) and classified according to ACE polymorphisms.

End point type	Secondary

End point timeframe:

From the beginning until the end of the study.

End point values	IN/DEL	IN/IN	DEL/DEL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	14	40	
Units: Subjects	9	3	7	

Statistical analyses

Statistical analysis title	Fisher`s exact test
Comparison groups	IN/DEL v IN/IN v DEL/DEL
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.941
Method	Fisher exact

Secondary: DCR according to ACE polymorphisms

End point title	DCR according to ACE polymorphisms

End point description:

Percentage of patients with either a complete response (CR), partial response (PR) or stable disease (SD) according to RECIST criteria (version 1.1) and classified according ACE polymorphisms.

End point type	Secondary

End point timeframe:

From the beginning until the end of the study.

End point values	IN/DEL	IN/IN	DEL/DEL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	14	40	
Units: Subjects	33	9	28	

Statistical analyses

Statistical analysis title	Fisher`s exact test
Comparison groups	IN/DEL v IN/IN v DEL/DEL
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.913
Method	Fisher exact

Secondary: PFS according to ACE polymorphisms

End point title	PFS according to ACE polymorphisms
End point description:	
PFS was defined as the time from inclusion to disease progression (observed radiologically) or death from any cause. Results a presented here according to ACE polymorphisms.	
End point type	Secondary
End point timeframe:	
From inclusion to disease progression or death from any cause.	

End point values	IN/DEL	IN/IN	DEL/DEL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	14	40	
Units: months				
median (confidence interval 95%)	9.0 (6.9 to 11.0)	4.3 (0.0 to 9.4)	7.4 (5.4 to 9.3)	

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	IN/DEL v IN/IN v DEL/DEL
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.854
Method	Logrank

Secondary: OS according to ACE polymorphisms

End point title	OS according to ACE polymorphisms
End point description:	
Time from inclusion to death from any cause according to ACE polymorphisms.	
End point type	Secondary
End point timeframe:	
From inclusion to death from any cause.	

End point values	IN/DEL	IN/IN	DEL/DEL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	14	40	
Units: months				
median (confidence interval 95%)	15.5 (11.0 to 20.0)	8.6 (0.7 to 16.5)	10.4 (7.3 to 13.4)	

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	IN/DEL v IN/IN v DEL/DEL
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.689
Method	Logrank

Secondary: TTP according to ACE polymorphisms

End point title	TTP according to ACE polymorphisms

End point description:

Time from inclusion to disease progression or death for progression according to ACE polymorphisms.

End point type	Secondary

End point timeframe:

From inclusion to disease progression or death for progression.

End point values	IN/DEL	IN/IN	DEL/DEL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	14	40	
Units: months				
median (confidence interval 95%)	9.0 (6.8 to 11.2)	4.3 (0.0 to 9.4)	7.4 (4.4 to 10.4)	

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	IN/DEL v IN/IN v DEL/DEL
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.828
Method	Logrank

Secondary: TTF according to ACE polymorphisms

End point title	TTF according to ACE polymorphisms
End point description:	
Time from inclusion to treatment discontinuation for any reason according to ACE polymorphisms.	
End point type	Secondary
End point timeframe:	
From inclusion to treatment discontinuation.	

End point values	IN/DEL	IN/IN	DEL/DEL	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	47	14	40	
Units: months				
median (confidence interval 95%)	7.1 (5.1 to 9.2)	4.5 (2.1 to 7.0)	5.4 (3.9 to 7.0)	

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	IN/DEL v IN/IN v DEL/DEL
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.477
Method	Logrank

Secondary: OS according to VEGF-A levels

End point title	OS according to VEGF-A levels
End point description:	
Time from inclusion to death from any cause according to VEGF-A levels.	
End point type	Secondary
End point timeframe:	
From inclusion to death from any cause.	

End point values	<1.941 ng/ml	≥1.941 ng/ml		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	47		
Units: months				
median (confidence interval 95%)	18.9 (14.8 to 23.0)	7.6 (4.5 to 10.7)		

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	<1.941 ng/ml v ≥1.941 ng/ml
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Logrank

Other pre-specified: PFS according to VEGF-A levels

End point title	PFS according to VEGF-A levels

End point description:

Time from inclusion to disease progression (observed radiologically) or death from any cause according to VEGF-A levels.

End point type	Other pre-specified

End point timeframe:

From inclusion to disease progression or death from any cause.

End point values	<1.941 ng/ml	≥1.941 ng/ml		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	53	47		
Units: months				
median (confidence interval 95%)	9.2 (8.4 to 10.0)	4.2 (2.7 to 5.6)		

Statistical analyses

Statistical analysis title	Log-Rank
Comparison groups	<1.941 ng/ml v ≥1.941 ng/ml

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.001
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The treatment safety profile was a secondary endpoint, assessed according to AEs recorded throughout the study and the incidence of dose adjustments and compliance of study treatment.

Adverse event reporting additional description:

The variables evaluated to characterize the AE profile of the treatment were their incidence and severity as per the NCI-CTCAE criteria (version 4.03).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 101 (36.63%)		
number of deaths (all causes)	65		
number of deaths resulting from adverse events	11		
Injury, poisoning and procedural complications			
Chemical peritonitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Ventricular dysfunction	Additional description: Left ventricular systolic dysfunction		
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hepatic encephalopathy			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
General disorders and administration site conditions			

Asthenia

subjects affected / exposed — 4 / 101 (3.96%)

occurrences causally related to treatment / all — 3 / 4

deaths causally related to treatment / all — 0 / 0

Death

subjects affected / exposed — 1 / 101 (0.99%)

occurrences causally related to treatment / all — 1 / 1

deaths causally related to treatment / all — 1 / 1

Pyrexia

Additional description: Febrile syndrome of persistent respiratory focus.

subjects affected / exposed — 1 / 101 (0.99%)

occurrences causally related to treatment / all — 0 / 1

deaths causally related to treatment / all — 0 / 0

General physical health deterioration

subjects affected / exposed — 6 / 101 (5.94%)

occurrences causally related to treatment / all — 1 / 6

deaths causally related to treatment / all — 0 / 5

Pain

subjects affected / exposed — 2 / 101 (1.98%)

occurrences causally related to treatment / all — 0 / 2

deaths causally related to treatment / all — 0 / 1

Blood and lymphatic system disorders

Febrile neutropenia

subjects affected / exposed — 1 / 101 (0.99%)

occurrences causally related to treatment / all — 1 / 1

deaths causally related to treatment / all — 0 / 0

Gastrointestinal disorders

Abdominal pain

subjects affected / exposed — 4 / 101 (3.96%)

occurrences causally related to treatment / all — 0 / 4

deaths causally related to treatment / all — 0 / 0

Colitis

subjects affected / exposed — 1 / 101 (0.99%)

occurrences causally related to treatment / all — 1 / 1

deaths causally related to treatment / all — 0 / 0

Diarrhoea

subjects affected / exposed	3 / 101 (2.97%)
occurrences causally related to treatment / all	3 / 3
deaths causally related to treatment / all	0 / 0

Dysphagia

subjects affected / exposed	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0

Enterocolitis

subjects affected / exposed	1 / 101 (0.99%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0

Gastrointestinal toxicity

subjects affected / exposed	1 / 101 (0.99%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	1 / 1

Intestinal obstruction

subjects affected / exposed	8 / 101 (7.92%)
occurrences causally related to treatment / all	0 / 8
deaths causally related to treatment / all	0 / 0

Large intestine perforation

subjects affected / exposed	1 / 101 (0.99%)
occurrences causally related to treatment / all	1 / 1
deaths causally related to treatment / all	0 / 0

Upper gastrointestinal haemorrhage

subjects affected / exposed	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0

Female genital tract fistula

subjects affected / exposed	1 / 101 (0.99%)
occurrences causally related to treatment / all	0 / 1
deaths causally related to treatment / all	0 / 0

Vomiting

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders

Bile duct stone

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders

Dyspnoea

subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

Pneumonitis

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory tract infection

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders

Acute kidney injury

subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Nephritic syndrome

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection

subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Subcutaneous abscess			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Anal abscess			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	101 / 101 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	37 / 101 (36.63%)		
occurrences (all)	76		
Nervous system disorders			
Headache			
subjects affected / exposed	22 / 101 (21.78%)		
occurrences (all)	40		
Neurotoxicity			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	7		
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	13 / 101 (12.87%)		
occurrences (all)	18		
Neutropenia			
subjects affected / exposed	45 / 101 (44.55%)		
occurrences (all)	136		
Thrombocytopenia			
subjects affected / exposed	8 / 101 (7.92%)		
occurrences (all)	27		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	75 / 101 (74.26%)		
occurrences (all)	282		
Fatigue			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	11		
General physical health deterioration			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	7		
Mucosal inflammation			
subjects affected / exposed	58 / 101 (57.43%)		
occurrences (all)	162		
Oedema peripheral			
subjects affected / exposed	8 / 101 (7.92%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	15 / 101 (14.85%)		
occurrences (all)	30		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	29 / 101 (28.71%)		
occurrences (all)	52		
Abdominal pain upper			

subjects affected / exposed	10 / 101 (9.90%)			
occurrences (all)	11			
Constipation				
subjects affected / exposed	19 / 101 (18.81%)			
occurrences (all)	22			
Diarrhoea				
subjects affected / exposed	78 / 101 (77.23%)			
occurrences (all)	283			
Dysgeusia				
subjects affected / exposed	14 / 101 (13.86%)			
occurrences (all)	18			
Dyspepsia				
subjects affected / exposed	7 / 101 (6.93%)			
occurrences (all)	9			
Intestinal obstruction				
subjects affected / exposed	6 / 101 (5.94%)			
occurrences (all)	8			
Nausea				
subjects affected / exposed	34 / 101 (33.66%)			
occurrences (all)	72			
Odynophagia				
subjects affected / exposed	8 / 101 (7.92%)			
occurrences (all)	9			
Proctalgia				
subjects affected / exposed	10 / 101 (9.90%)			
occurrences (all)	23			
Rectal haemorrhage				
subjects affected / exposed	8 / 101 (7.92%)			
occurrences (all)	12			
Stomatitis				
subjects affected / exposed	7 / 101 (6.93%)			
occurrences (all)	13			
Vomiting				
subjects affected / exposed	30 / 101 (29.70%)			
occurrences (all)	46			
Respiratory, thoracic and mediastinal				

disorders			
Aphonia			
subjects affected / exposed	9 / 101 (8.91%)		
occurrences (all)	10		
Dysphonia			
subjects affected / exposed	24 / 101 (23.76%)		
occurrences (all)	37		
Dyspnoea			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	11		
Epistaxis			
subjects affected / exposed	31 / 101 (30.69%)		
occurrences (all)	50		
Nasopharyngitis			
subjects affected / exposed	10 / 101 (9.90%)		
occurrences (all)	10		
Respiratory tract infection			
subjects affected / exposed	9 / 101 (8.91%)		
occurrences (all)	12		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	22 / 101 (21.78%)		
occurrences (all)	29		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	9		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	9 / 101 (8.91%)		
occurrences (all)	10		
Proteinuria			
subjects affected / exposed	10 / 101 (9.90%)		
occurrences (all)	16		
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	10 / 101 (9.90%)		
occurrences (all)	12		
Musculoskeletal pain			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	10		
Metabolism and nutrition disorders Decreased appetite			
subjects affected / exposed	31 / 101 (30.69%)		
occurrences (all)	48		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

These preliminary results are exploratory and further analysis are required.

Notes: