Clinical trial results:
A Global, Multicenter, Randomized, Placebo-Controlled Phase 3 Trial to Compare the Efficacy and Safety of Fruquintinib Plus Best Supportive Care to Placebo Plus Best Supportive Care in Patients with Refractory Metastatic Colorectal Cancer (FRESCO-2)

Summary

EudraCT number	2020-000158-88
Trial protocol	HU FR DE AT BE IT CZ PL
Global end of trial date	24 April 2024

Results information

Result version number	v1 (current)
This version publication date	21 March 2025
First version publication date	21 March 2025

Trial information

Trial identification

Sponsor protocol code	2019-013-GLOB1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04322539
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hutchison MediPharma Limited
Sponsor organisation address	Building 4, 720 Cailun Road, Shanghai, China, 201203
Public contact	William Schelman, HUTCHMED International, +1 973-306-4490, williams@hutch-med.com
Scientific contact	William Schelman, HUTCHMED International , +1 973-306-4490, williams@hutch-med.com

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	24 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this was to evaluate the overall survival of Fruquintinib plus best supportive care (BSC) compared to placebo plus BSC in subjects with refractory metastatic colorectal cancer (mCRC).

Protection of trial subjects:

The study was conducted in accordance with the protocol; the ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines; applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines; and other applicable regulations and guidelines governing clinical study conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 August 2020
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	Australia: 16
Country: Number of subjects enrolled	Japan: 56
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 124
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Czechia: 14
Country: Number of subjects enrolled	Estonia: 9
Country: Number of subjects enrolled	France: 64
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Hungary: 69
Country: Number of subjects enrolled	Italy: 111
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 180
Worldwide total number of subjects	691
EEA total number of subjects	492

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)	366
From 65 to 84 years	324
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 124 study sites in the United States, Europe region, Japan, and Australia.

Pre-assignment

Screening details:

A total of 691 subjects were randomized and treated in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fruquintinib + Best Supportive Care (BSC) Group

Arm description:

Subjects received 5 milligrams (mg) of fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).

Arm type	Experimental
Investigational medicinal product name	Fruquintinib 5 mg
Investigational medicinal product code	
Other name	HMPL-013
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received 5 mg of fruquintinib oral capsule in combination with BSC once daily for 3 weeks.

Arm title	Placebo + BSC Group

Arm description:

Subjects received placebo matched to fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).

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

Dosage and administration details:

Subjects received placebo matched to fruquintinib oral capsule in combination with BSC once daily for 3 weeks.

Number of subjects in period 1	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group
Started	461	230
Safety Population (SP)	456	230
Pharmacokinetic (PK) Population	329	2
Completed	0	0
Not completed	461	230
Consent withdrawn by subject	14	8
Adverse event, non-fatal	2	-
Death	411	203
Sponsor Decision	19	14
Unspecified	6	4
Radiological Disease Progression	6	-
Lost to follow-up	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Fruquintinib + Best Supportive Care (BSC) Group
Reporting group description:	
Subjects received 5 milligrams (mg) of fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).	
Reporting group title	Placebo + BSC Group
Reporting group description:	
Subjects received placebo matched to fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).	

Reporting group values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group	Total
Number of subjects	461	230	691
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	62.2	62.4	
standard deviation	± 10.41	± 9.67	-
Gender categorical Units: Subjects			
Female	216	90	306
Male	245	140	385
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	43	18	61
Black or African American	13	7	20
Native Hawaiian or Other	3	2	5
White	367	192	559
Other	5	2	7
Multiple races	2	0	2
Not reported/unknown	28	8	36
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	20	14	34
Not Hispanic or Latino	405	202	607
Unknown or Not Reported	36	14	50

End points

End points reporting groups

Reporting group title	Fruquintinib + Best Supportive Care (BSC) Group

Reporting group description:

Subjects received 5 milligrams (mg) of fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).

Reporting group title	Placebo + BSC Group

Reporting group description:

Subjects received placebo matched to fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).

Subject analysis set title	Fruquintinib:Pooled Studies for Exposure and Safety Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in the current 2019-013-GLOB1 study received 5 mg of fruquintinib oral capsules once daily for 3 weeks of continuous dosing, followed by a 1-week break during each 28-day treatment cycle. Subjects in the 2009-013-00CH1 study received 1 mg to 6 mg of fruquintinib oral capsule once daily and 5 mg to 6 mg of fruquintinib oral capsule for 3 weeks on and 1 week off during each 28-day treatment cycle. Subjects in the 2012-013-00CH3 study received 4 mg of fruquintinib capsule once daily in 28-day cycles. Subjects in the Study 2015-013- 00US1 with advanced solid tumors of any type or with mCRC received fruquintinib 3 mg or 5 mg once daily for 3 weeks on and 1 week off in each 28-day treatment cycle until disease progression, unacceptable toxicity, use of other antitumor treatment, withdrawal of consent, or discontinuation by the Investigator, whichever occurred first.

Subject analysis set title	Fruquintinib:Pooled Studies for Exposure and Efficacy Analysis
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects in the current 2019-013-GLOB1 study received 5 mg of fruquintinib oral capsules once daily for 3 weeks of continuous dosing, followed by a 1-week break during each 28-day treatment cycle. Subjects in Cohort B of Study 2015-013-00US1 with metastatic colorectal carcinoma (mCRC) and prior treatment with chemotherapy and trifluridine, tipiracil, and/or regorafenib received fruquintinib 5 mg capsules once daily for 3 weeks on and 1 week off in each 28-day treatment cycle until disease progression, unacceptable toxicity, use of other antitumor treatment, withdrawal of consent, or discontinuation by the Investigator, whichever occurred first.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time (months) from date of randomization to death from any cause. OS was calculated as (date of death or last known alive – date of randomization + 1)/30.4375. Subjects without report of death at the time of analysis will be censored at the date last known alive. Intent to treat (ITT) population included all randomized subjects.

End point type	Primary

End point timeframe:

From date of randomization to death from any cause (up to 22 months)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	230		
Units: months				
median (confidence interval 95%)	7.4 (6.7 to 8.2)	4.8 (4.0 to 5.8)		

Statistical analyses

Statistical analysis title	Fruquintinib + BSC Group Vs Placebo + BSC Group
Comparison groups	Fruquintinib + Best Supportive Care (BSC) Group v Placebo + BSC Group
Number of subjects included in analysis	691
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [1]
Method	stratified log-rank test
Parameter estimate	Stratified Hazard ratio
Point estimate	0.662
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.549
upper limit	0.8

Notes:

[1] - Raw unadjusted p-value was obtained by using a stratified log-rank test accounting for the randomization schedule stratification factors.

Secondary: Progression Free Survival (PFS), as Assessed by the Investigator Using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1

End point title	Progression Free Survival (PFS), as Assessed by the Investigator Using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1

End point description:

PFS was defined as the time (months) from randomization until the first radiographic documentation of objective progression as assessed by investigator using RECIST v1.1, or death from any cause, whichever comes first. More specifically, PFS was determined using all data until the last evaluable visit prior to or on the date of: (i) radiographic disease progression (PD) per RECIST v1.1; (ii) withdrawal of consent to obtain additional scans on study; or (iii) initiation of subsequent anticancer therapy other than the study drugs, whichever was earlier. PD was defined as: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline; an absolute increase of at least 5 mm in the sum of diameters of target lesions; and the appearance of one or more new lesions. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization until the first documentation of objective progression or death, whichever comes first (up to 22 months)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	230		
Units: months				
median (confidence interval 95%)	3.7 (3.5 to 3.8)	1.8 (1.8 to 1.9)		

Statistical analyses

Statistical analysis title	Fruquintinib + BSC Group Vs Placebo + BSC Group
Comparison groups	Placebo + BSC Group v Fruquintinib + Best Supportive Care (BSC) Group
Number of subjects included in analysis	691
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	stratified log-rank test
Parameter estimate	Stratified Hazard ratio
Point estimate	0.321
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.267
upper limit	0.386

Notes:

[2] - Raw unadjusted p-value was obtained by using a stratified log-rank test accounting for the randomization schedule stratification factors.

Secondary: Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Objective Response Rate (ORR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

ORR was defined as the percentage of subjects who achieved a best overall response of confirmed complete response (CR) or partial response (PR), per RECIST v1.1, as determined by the investigator. PR: At least a 30 percent (%) decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to less than (<)10 millimeters (mm). ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization until PD, death, new anticancer treatment, or study treatment discontinuation, whichever occurred first (up to 22 months)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	230		
Units: percentage of subjects				
number (confidence interval 95%)	1.5 (0.6 to 3.1)	0 (0.0 to 1.6)		

Statistical analyses

Statistical analysis title	Fruquintinib + BSC Group Vs Placebo + BSC Group
Comparison groups	Fruquintinib + Best Supportive Care (BSC) Group v Placebo + BSC Group
Number of subjects included in analysis	691
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.059 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.7

Notes:

[3] - The adjusted difference and its 95% CI were calculated using the Wald method from Cochran-Mantel Haenszel test to account for the randomization schedule stratification factors.
[4] - p-value was calculated from a stratified Cochran-Mantel Haenszel test accounting for the randomization schedule stratification factors.

Secondary: Disease Control Rate (DCR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Disease Control Rate (DCR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

DCR was defined as percentage of subjects achieving a best overall response of confirmed CR, PR, or stable disease (SD) (for at least 7 weeks) per RECIST v1.1, as determined by the investigator. PR: At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum on study. PD: At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From randomization until PD, death, new anticancer treatment, or study treatment discontinuation, whichever occurred first (up to 22 months)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	230		
Units: percentage of subjects				
number (confidence interval 95%)	55.5 (50.9 to 60.1)	16.1 (11.6 to 21.5)		

Statistical analyses

Statistical analysis title	Fruquintinib + BSC Group Vs Placebo + BSC Group
Comparison groups	Fruquintinib + Best Supportive Care (BSC) Group v Placebo + BSC Group
Number of subjects included in analysis	691
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Adjusted difference
Point estimate	39.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	32.8
upper limit	46

Notes:

[5] - p-value was calculated from a stratified Cochran-Mantel Haenszel test accounting for the randomization schedule stratification factors.

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) and Serious TEAEs

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE was considered a TEAE if the onset date was on or after the start of study treatment or if the onset date was missing, or if the AE had an onset date before the start of study treatment but worsened in severity after the study treatment until 30 days after the last dose of study treatment or a new treatment of anti-tumor therapy, whichever was earlier. After this period, treatment-related SAEs were also considered as TEAEs. AEs with an unknown/not reported onset date were also included. SP included all randomized subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

From start of study drug administration up to approximately 40 months

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	456	230		
Units: Count of subjects				
Subjects with TEAEs	451	214		
Subjects with Serious TEAEs	173	88		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Plasma Concentrations of Fruquintinib and Metabolite M11

End point title	Observed Plasma Concentrations of Fruquintinib and Metabolite M11[6]

End point description:

Plasma samples were collected from the subjects at the defined time points. Plasma concentrations were measured using a validated, specific, and sensitive liquid chromatography tandem mass spectrometry method. M11 is the active metabolite for the study drug. PK population was used for tabulation of fruquintinib and M11 concentrations from PK plasma samples collected from the Fruquintinib + BSC Group. PK samples for the Placebo + BSC Group were not analyzed. Here "N"=subjects evaluable for this endpoint; "n"=subjects evaluable at the specified timepoints. Here "C" indicates "Cycle", "D" indicates "Day" an "Conc." indicates "Concentration". Here "99999" indicates "Standard deviation", was not evaluable for single subject.

End point type	Secondary

End point timeframe:

Cycle 1 (Day 1 and 21): Pre-dose, 1, 2, 3 and 4 hours; Cycle 2 (Day 21): Predose and 2 hours, Cycle 3 (Day 1): Pre-dose, Cycle 3 (Day 21): Pre-dose and 2 hours, Cycle 5, 7, 9, 11, 13, 15 and 17 (Day 1): Pre-dose (Each cycle = 28 days)

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: As per planned analysis, data for this endpoint was analysed for Fruquintinib arm only.

End point values	Fruquintinib + Best Supportive Care (BSC) Group			
Subject group type	Reporting group			
Number of subjects analysed	312			
Units: nanogram/milliliter (ng/mL)				
arithmetic mean (standard deviation)				
C1D1:1 hour (Plasma Conc. of Fruquintinib)(n=171)	59.9 (± 51.0)			
C1D1:1 hour (Plasma Conc. of M11)(n=171)	1.06 (± 8.36)			
C1D1:2 hours (Plasma Conc. of Fruquintinib)(n=304)	91.5 (± 48.2)			
C1D1:2 hours (Plasma Conc. of M11)(n=304)	1.03 (± 6.81)			
C1D1:3 hours (Plasma Conc. of Fruquintinb)(n=171)	98.5 (± 47.1)			

C1D1:3 hours (Plasma Conc. of M11)(n=171)	1.96 (± 9.51)			
C1D1:4 hours (Plasma Conc. of Fruquintinb)(n=171)	99.7 (± 44.6)			
C1D1:4 hours (Plasma Conc. of M11)(n=171)	2.71 (± 10.7)			
C1D21:Predose(Plasma Conc. of Fruquintinib)(n=227)	219 (± 82.6)			
C1D21:Predose (Plasma Conc. of M11)(n=227)	94.5 (± 52.6)			
C1D21:1 hour (Plasma Conc. of Fruquintinib)(n=112)	255 (± 101)			
C1D21:1 hour (Plasma Conc. of M11)(n=112)	92.0 (± 54.3)			
C1D21:2 hours(Plasma Conc. of Fruquintinib)(n=214)	279 (± 91.6)			
C1D21:2 hours (Plasma Conc. of M11)(n=214)	89.9 (± 49.5)			
C1D21:3 hours(Plasma Conc. of Fruquintinib)(n=113)	293 (± 95.2)			
C1D21:3 hours (Plasma Conc. of M11)(n=113)	88.0 (± 50.4)			
C1D21:4 hours(Plasma Conc. of Fruquintinib)(n=114)	294 (± 88.0)			
C1D21:4 hours (Plasma Conc. of M11)(n=114)	89.2 (± 49.0)			
C2D21:Predose(Plasma Conc. of Fruquintinib)(n=204)	222 (± 82.0)			
C2D21:Predose (Plasma Conc. of M11)(n=204)	97.6 (± 53.7)			
C2D21:2 hours(Plasma Conc. of Fruquintinib)(n=193)	284 (± 95.2)			
C2D21:2 hours (Plasma Conc. of M11)(n=193)	94.2 (± 52.8)			
C3D1:Predose(Plasma Conc. of Fruquintinib)(n=177)	16.7 (± 18.9)			
C3D1:Predose (Plasma Conc. of M11)(n=177)	22.6 (± 18.2)			
C3D21:Predose(Plasma Conc. of Fruquintinib)(n=137)	212 (± 74.6)			
C3D21:Predose (Plasma Conc. of M11)(n=137)	90.6 (± 54.1)			
C3D21:2 hours(Plasma Conc. of Fruquintinib)(n=123)	275 (± 78.6)			
C3D21:2hours (Plasma Conc. of M11)(n=123)	92.8 (± 54.2)			
C5D1:Predose(Plasma Conc. of Fruquintinib)(n=103)	16.9 (± 20.5)			
C5D1:Predose (Plasma Conc. of M11)(n=103)	23.2 (± 20.9)			
C7D1:Predose(Plasma Conc. of Fruquintinib)(n=46)	18.2 (± 33.0)			
C7D1:Predose (Plasma Conc. of M11)(n=46)	20.1 (± 12.1)			
C9D1:Predose(Plasma Conc. of Fruquintinib)(n=13)	12.2 (± 12.6)			
C9D1:Predose (Plasma Conc. of M11)(n=13)	19.1 (± 17.1)			
C11D1:Predose (Plasma Conc. of Fruquintinib)(n=6)	13.4 (± 13.4)			
C11D1:Predose (Plasma Conc. of M11)(n=6)	17.1 (± 15.3)			

C13D1:Predose (Plasma Conc. of Fruquintinib)(n=1)	15.4 (± 99999)			
C13D1:Predose (Plasma Conc. of M11)(n=1)	23.1 (± 99999)			
C15D1:Predose (Plasma Conc. of Fruquintinib)(n=1)	10.8 (± 99999)			
C15D1:Predose (Plasma Conc. of M11)(n=1)	19.2 (± 99999)			
C17D1:Predose (Plasma Conc. of Fruquintinib)(n=1)	10.6 (± 99999)			
C17D1:Predose (Plasma Conc. of M11)(n=1)	15.2 (± 99999)			
C1D1:Predose (Plasma Conc. of Fruquintinib)(n=312)	2.90 (± 19.9)			
C1D1:Predose (Plasma Conc. of M11)(n=312))	0.585 (± 6.61)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point title	Duration of Response (DOR) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1)

End point description:

DOR was defined as the time (in months) from the first occurrence of PR or CR by RECIST Version 1.1, until the first date that progressive disease is documented by RECIST Version 1.1, or death, whichever comes first. Only those subjects with confirmed responses of CR or PR were included in this analysis. DOR was calculated as (date of death or PD or last assessment – date of first occurrence of confirmed CR or PR + 1)/30.4375. Analysis was performed on subset of subjects who had a response. Here, '0' in 'overall number of subjects analyzed represents that DOR could only be analyzed in subjects who achieved a response. As no subject in the Placebo Plus BSC Group cohort achieved any response, no DOR is available. Here "99999" means upper limit of 95 percent (%) confidence interval (CI) was not estimable due to limited number of subjects with events.

End point type	Secondary

End point timeframe:

From first occurrence of PR or CR until the first documentation of progression or death, whichever comes first (up to 22 months)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	0[7]		
Units: months				
median (confidence interval 95%)	10.7 (3.9 to 99999)	(to)		

Notes:

[7] - Since no subject in the Placebo Plus BSC Group cohort achieved any response, no DOR is available.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of Electrocardiogram (ECG) Results - QTcF Intervals Using Fridericia's Formula

End point title	Change From Baseline of Electrocardiogram (ECG) Results - QTcF Intervals Using Fridericia's Formula

End point description:

QT Interval: Ventricular depolarization plus ventricular repolarization Normal Range: 400 to 460 milliseconds (msec). QTc: QT interval corrected based on the patient's heart rate. QTcF: An electrocardiographic finding in which the QT interval corrected for heart rate using Fridericia's formula. QTc = QT/(RR) RR = Respiration rate. SP included all randomized subjects who received at least 1 dose of study drug. Here "N"=subjects evaluable for this endpoint; "n"=subjects evaluable at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Cycle 1 (Day 1 and 21): Pre-dose, 1, 2, 3 and 4 hours; Cycle 2 and 3 (Day 21): Pre-dose (Each cycle = 28 days)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	131		
Units: millisecond (msec)				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 - Pre-dose (n=261,126)	1.9 (± 21.33)	0.1 (± 17.95)		
Cycle 1 Day 1 - 1 hour (n=149,71)	-0.1 (± 19.60)	2.5 (± 19.70)		
C1D1-2 hours(n=272,131)	1.9 (± 22.58)	3.5 (± 20.13)		
C1D1-3 hours (n=143,70)	2.6 (± 19.77)	3.3 (± 18.03)		
C1D1-4 hours (n=136,67)	1.2 (± 20.48)	0.9 (± 17.66)		
C1D21-Pre-dose (n=184,95)	3.2 (± 20.94)	-2.2 (± 20.31)		
C1D21-1 hour (n=109,62)	4.0 (± 19.56)	-0.2 (± 16.77)		
C1D21-2 hours (n=222,121)	5.0 (± 20.06)	2.8 (± 18.23)		
C1D21-3 hours (n=111,61)	5.9 (± 19.46)	0.2 (± 14.70)		
C1D21-4 hours (n=103,58)	3.9 (± 20.98)	-0.6 (± 18.13)		
C2D21-2 hours (n=229,86)	1.4 (± 22.41)	4.9 (± 24.28)		
C3D21-2 hours (n=141,28)	2.6 (± 31.61)	2.0 (± 20.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline of ECG Results -QTcB Intervals Using Bazzett's Formula

End point title	Change From Baseline of ECG Results -QTcB Intervals Using Bazzett's Formula

End point description:

QT Interval: Ventricular depolarization plus ventricular repolarization Normal Range: 400 to 460 msec. QTc: QT interval corrected based on the patient's heart rate. QTcB: An electrocardiographic finding in which the QT interval corrected for heart rate using Bazzett's formula. SP included all randomized subjects who received at least 1 dose of study drug. Here "N"=subjects evaluable for this endpoint; "n"=subjects evaluable at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Cycle 1 (Day 1 and 21): Pre-dose, 1, 2, 3 and 4 hours; Cycle 2 and 3 (Day 21): Pre-dose (Each cycle = 28 days)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	122		
Units: msec				
arithmetic mean (standard deviation)				
C1D1-Pre-dose (n=249,118)	2.9 (± 39.49)	0.3 (± 20.55)		
C1D1-1 hour (n=142,69)	-3.1 (± 23.95)	1.9 (± 20.11)		
C1D1-2 hours (n=258,122)	-2.0 (± 23.95)	1.9 (± 20.11)		
C1D1-3 hours (n=136,68)	-0.9 (± 24.47)	3.9 (± 19.75)		
C1D1-4 hours (n=130,65)	-1.9 (± 24.47)	2.4 (± 20.11)		
C1D21-Pre-dose (n=177,91)	3.9 (± 49.99)	5.0 (± 50.43)		
C1D21-1 hour (n=177,60)	-1.3 (± 25.60)	0.9 (± 20.48)		
C1D21-2 hours (n=212,117)	1.6 (± 42.28)	4.3 (± 19.57)		
C1D21-3 hours (n=107,59)	1.2 (± 25.41)	2.9 (± 18.29)		
C1D21-4 hours (n=99,56)	0.2 (± 25.91)	2.8 (± 20.13)		
C2D21-2 hours (n=213,83)	1.7 (± 40.61)	5.9 (± 24.96)		
C3D21-2 hours (n=132,28)	4.2 (± 72.35)	1.6 (± 22.06)		

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Fruquintinib Exposure (CmaxSS) and Safety Parameters (Any Grade [Gr] and Grade 3+ [Gr3+]: Dermatological Toxicity, Proteinuria and Gr Hemorrhage)

End point title	Correlation Between Fruquintinib Exposure (CmaxSS) and Safety Parameters (Any Grade [Gr] and Grade 3+ [Gr3+]: Dermatological Toxicity, Proteinuria and Gr Hemorrhage)

End point description:

Model-predicted steadystate maximum plasma concentration (CmaxSS) of fruquintinib based on assigned dose investigated as fruquintinib exposure measure for safety exposure-response (E-R) analysis. Correlation between exposure and probability of experiencing AEs evaluated using logistic regression analysis, with slope serving as estimate. Safety E-R analysis included subjects from 2019-013-GLOB1, 2009-013-00CH1, 2012-013-00CH3, and 2015-013-00US1. "Unit"i.e.,'1/(nanogram per milliliter)' corresponds to the coefficient that describes the relationship between probability of occurrence of safety parameter and CmaxSS value. Safety E-R analyses had subjects evaluable for population PK analysis,PK parameter estimates to enable estimation of fruquintinib exposure and

evaluated for endpoint in question."N"=subjects evaluable for this endpoint;"n"=subjects evaluable at specified timepoints. The population included subjects from 2019-013- GLOB1, 2009-013- 00CH1, 212-013-00CH3, and 2015-013-00US.

End point type	Secondary

End point timeframe:

Up to 22 months

End point values	Fruquintinib:Pooled Studies for Exposure and Safety Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	515			
Units: 1/ (nanogram per milliliter)				
number (not applicable)				
CmaxS S Coefficient for Any G Derma Toxicity	0.00134			
CmaxSS Coefficient for G3+ Derma Toxicity	0.00411			
CmaxSS Coefficient for Any G Proteinuria	-0.0010			
CmaxSS Coefficient for G3+ Proteinuria	0.00143			
CmaxSS Coefficient for Any G Hemorrhage	0.00180			

Statistical analyses

No statistical analyses for this end point

Secondary: Correlation Between Fruquintinib Exposure (CminSS) and Efficacy Parameters (OS)

End point title	Correlation Between Fruquintinib Exposure (CminSS) and Efficacy Parameters (OS)

End point description:

Model-predicted steady-state minimum plasma concentrations (CminSS) of fruquintinib based on starting dose or adjusted for relative dose intensity(RDI) used as exposure measures in efficacy exposure-response analyses. Correlation between OS and exposure estimated using multivariable Cox proportional hazards modeling with OS analyzed as time-to-event variable using survival model. Analysis included subjects from 2019-013-GLOB1(N=328) and Cohort B of 2015-013-00US1(N=40). "Unit" i.e., '1/(nanogram per milliliter)', corresponds to the coefficient that describes the relationship between probability of survival and CminSS value. Efficacy exposure- response analyses included subjects evaluable for population PK analysis, had PK parameter estimates to enable estimation of fruquintinib exposure and evaluated for parameter in question. "N" = subjects evaluable for this endpoint; "n"= subjects evaluable at specified timepoints. Population included subjects from 2015-013-00US1 and current study.

End point type	Secondary

End point timeframe:

Up to 22 months

End point values	Fruquintinib:Pooled Studies for Exposure and Efficacy Analysis			
Subject group type	Subject analysis set			
Number of subjects analysed	368			
Units: 1/ (nanogram per milliliter)				
number (not applicable)				
CminSS Coefficient Based on Starting Dose	0.00193			
CminSS Coefficient Based on Adjusted RDI	0.000407			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life (QOL) Questionnaire Core 30 (EORTC QLQ-C30) Global Health Status/Quality of Life Scale Score

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer Quality of Life (QOL) Questionnaire Core 30 (EORTC QLQ-C30) Global Health Status/Quality of Life Scale Score

End point description:

EORTC QLQ-C30 contains 30 items across 5 functional scales(physical, role, cognitive, emotional, and social), 9 symptom scales(fatigue,nausea and vomiting,pain,dyspnea, sleep disturbance,appetite loss,constipation,diarrhea, and financial difficulties)and global health status/QOL scale. EORTC QLQ-C30 contains 28 questions(4-point scale where 1=Not at all [best] to 4=Very Much [worst]) and 2 questions(7-point scale where 1=Very poor [worst] to 7= Excellent [best]).Raw scores are standardized and converted into scale scores ranging from 0-100. For global health status/QOL scale, higher scores=better QOL.Negative change from baseline=condition worsened.Change from baseline in the EORTC QLQ-C30 Global Health Status/Quality of Life Scale scores was performed by visit (i.e., cycle), using restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach. ITT population. "N"=subjects evaluable for this endpoint; "n"=subjects evaluable at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2, 3 and 4 (Each cycle=28 days)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	330	149		
Units: score on a scale				
least squares mean (standard error)				
Cycle 2 (n=330,149)	-2.1 (± 1.59)	-3.7 (± 1.95)		
Cycle 3 (n=229, 53)	-4.5 (± 1.69)	-6.1 (± 2.54)		
Cycle 4 (n=182,29)	-4.2 (± 1.76)	-2.1 (± 3.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL 5 Dimension 5 Level (EQ-5D-5L) Visual Analog Scale (VAS) Score

End point title	Change From Baseline in EuroQoL 5 Dimension 5 Level (EQ-5D-5L) Visual Analog Scale (VAS) Score

End point description:

The EQ-5D-5L is a self-reported health status questionnaire that consisted of six questions used to calculate a health utility score. There were two components to the EQ-5D-5L: a five-item health state profile that assessed mobility, self-care, usual activities, pain/discomfort, and anxiety/depression used to obtain an Index Utility Score and a general VAS score for health status. EQ-5D VAS was used to record subjects's rating for his/her current health-related quality of life state on a vertical VAS with scores ranging from 0 to 100, where 0 = worst imaginable health state and 100 = best imaginable health state. The higher the score the better the health status. A negative change from baseline value represents patient condition worsened. Change from baseline in the EQ-5D-5L VAS scores was performed by visit (i.e. cycle), using a REML-based MMRM approach. ITT population. "N"=subjects evaluable for this endpoint; "n"=subjects evaluable at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2, 3 and 4 (Each cycle=28 days)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	151		
Units: score on a scale				
least squares mean (standard error)				
Cycle 2 (n=337,151)	-0.3 (± 1.38)	-0.9 (± 1.69)		
Cycle 3 (n=232,54)	-1.1 (± 1.48)	-2.5 (± 2.22)		
Cycle 4 (n=185,30)	-4.0 (± 1.59)	-2.1 (± 2.79)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Care Resource Utilization: Duration of Hospital Visits by Subjects

End point title	Health Care Resource Utilization: Duration of Hospital Visits by Subjects

End point description:

Duration of hospital visit was calculated as = stop date – start date + 1. Mean and standard deviation data for duration of hospital visits (in days) by subjects was reported in this endpoint. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 22 months

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	230		
Units: days per visit				
arithmetic mean (standard deviation)	3.3 (± 6.81)	4.4 (± 7.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Health Care Resource Utilization: Number of Subjects With Any Concomitant Medications Prescribed

End point title	Health Care Resource Utilization: Number of Subjects With Any Concomitant Medications Prescribed

End point description:

Number of subjects with any concomitant medications prescribed were reported. ITT population included all randomized subjects.

End point type	Secondary

End point timeframe:

From start of study drug administration up to 22 months

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	461	230		
Units: Subjects	116	63		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL 5 Dimension 5 Level (EQ-5D-5L) Health Utility Index Scores

End point title	Change From Baseline in EuroQoL 5 Dimension 5 Level (EQ-5D-5L) Health Utility Index Scores

End point description:

EQ-5D-5L consisted of 2 components: health state profile and optional VAS. EQ-5D health state profile had 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. Each dimension has 5 levels: 1= no problem, 2= slight problem, 3= moderate problem, 4= severe problem, and 5= extreme problem. The response levels collected from the EQ-5D-5L five dimensions as a health profile are converted into an EQ-5D-5L index (utility) scores to represent participants' utility value. Range of health utility index score is from -0.285 to 1, where higher value indicates perfect health and a negative value represents a state worse than dead. Change from baseline in EQ-5D-5L health utility index scores was performed by visit (i.e., cycle), using a REML-based MMRM approach. ITT population. "N"=subjects evaluable for this endpoint; "n"=subjects evaluable at the specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Cycle 2, 3 and 4 (Each cycle=28 days)

End point values	Fruquintinib + Best Supportive Care (BSC) Group	Placebo + BSC Group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	337	151		
Units: score on a scale				
least squares mean (standard error)				
Cycle 2 (n=337,151)	0.0 (± 0.01)	0.0 (± 0.02)		
Cycle 3 (n=232,54)	0.0 (± 0.01)	0.0 (± 0.02)		
Cycle 4 (n=185,30)	-0.1 (± 0.02)	0.0 (± 0.03)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration up to approximately 40 months

Adverse event reporting additional description:

All-Cause Mortality, Serious AEs and Non-Serious AEs data were collected based on safety population that included randomized subjects who received at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Placebo + BSC Group

Reporting group description:

Subjects received placebo matched to fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).

Reporting group title	Fruquintinib + BSC Group

Reporting group description:

Subjects received 5 mg of fruquintinib oral capsule in combination with BSC once daily for 3 weeks of continuous dosing followed by a 1-week break during a treatment cycle (Each cycle length was 28 days).

Serious adverse events	Placebo + BSC Group	Fruquintinib + BSC Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	88 / 230 (38.26%)	173 / 456 (37.94%)	
number of deaths (all causes)	203	408	
number of deaths resulting from adverse events	45	49	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	2 / 230 (0.87%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to meninges			

subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastasis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tumour invasion			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neoplasm progression			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Malignant neoplasm progression			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour associated fever			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 230 (0.00%)	6 / 456 (1.32%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	28 / 230 (12.17%)	27 / 456 (5.92%)	
occurrences causally related to treatment / all	0 / 32	0 / 28	
deaths causally related to treatment / all	0 / 27	0 / 26	
General physical health deterioration			
subjects affected / exposed	5 / 230 (2.17%)	10 / 456 (2.19%)	
occurrences causally related to treatment / all	0 / 7	0 / 13	
deaths causally related to treatment / all	0 / 2	0 / 2	
Asthenia			
subjects affected / exposed	0 / 230 (0.00%)	5 / 456 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			

subjects affected / exposed	2 / 230 (0.87%)	4 / 456 (0.88%)	
occurrences causally related to treatment / all	2 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	2 / 230 (0.87%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Death			
subjects affected / exposed	2 / 230 (0.87%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Non-cardiac chest pain			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Discomfort			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pain			

subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised Odema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermenstrual bleeding			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchopleural fistula			

subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 230 (0.87%)	6 / 456 (1.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 230 (0.00%)	5 / 456 (1.10%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchospasm			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			

subjects affected / exposed	2 / 230 (0.87%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 230 (0.87%)	4 / 456 (0.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Sternal fracture			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Recall phenomenon			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 230 (0.00%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 230 (0.43%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 230 (0.43%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Headache			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Polycythaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 230 (0.43%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	0 / 230 (0.00%)	4 / 456 (0.88%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 230 (0.43%)	5 / 456 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	6 / 230 (2.61%)	7 / 456 (1.54%)	
occurrences causally related to treatment / all	1 / 7	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 230 (0.87%)	7 / 456 (1.54%)	
occurrences causally related to treatment / all	1 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal pain upper			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	2 / 230 (0.87%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stomatitis			
subjects affected / exposed	1 / 230 (0.43%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Small intestinal perforation			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal perforation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			

subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic fistula			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 230 (0.00%)	4 / 456 (0.88%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	1 / 1	
Diarrhoea			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	5 / 230 (2.17%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 230 (0.00%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	3 / 230 (1.30%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal obstruction			

subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	2 / 230 (0.87%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal perforation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal stenosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovesical fistula			

subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	1 / 230 (0.43%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cholangitis			
subjects affected / exposed	1 / 230 (0.43%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	2 / 230 (0.87%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cholecystitis			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			

subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice			
subjects affected / exposed	2 / 230 (0.87%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic function abnormal			
subjects affected / exposed	2 / 230 (0.87%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 3	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bile duct stone			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stenosis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Urinary tract obstruction			
subjects affected / exposed	0 / 230 (0.00%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 230 (0.43%)	5 / 456 (1.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proteinuria			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vesicocutaneous fistula			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hypothyroidism			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	1 / 230 (0.43%)	6 / 456 (1.32%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			
subjects affected / exposed	0 / 230 (0.00%)	2 / 456 (0.44%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 230 (0.43%)	9 / 456 (1.97%)	
occurrences causally related to treatment / all	0 / 1	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 3	
Sepsis			
subjects affected / exposed	0 / 230 (0.00%)	5 / 456 (1.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abscess limb			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 230 (1.30%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fournier's gangrene			

subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 230 (0.43%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			

subjects affected / exposed	3 / 230 (1.30%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Wound sepsis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection bacterial			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronavirus infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 230 (0.00%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 230 (0.43%)	3 / 456 (0.66%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			

subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 230 (0.00%)	1 / 456 (0.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 456 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + BSC Group	Fruquintinib + BSC Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	205 / 230 (89.13%)	446 / 456 (97.81%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	21 / 230 (9.13%)	166 / 456 (36.40%)	
occurrences (all)	24	274	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	37 / 230 (16.09%)	93 / 456 (20.39%)	
occurrences (all)	41	139	
Asthenia			
subjects affected / exposed	52 / 230 (22.61%)	153 / 456 (33.55%)	
occurrences (all)	75	304	
Pyrexia			

subjects affected / exposed	22 / 230 (9.57%)	43 / 456 (9.43%)	
occurrences (all)	25	58	
Mucosal inflammation			
subjects affected / exposed	6 / 230 (2.61%)	62 / 456 (13.60%)	
occurrences (all)	7	97	
Oedema peripheral			
subjects affected / exposed	17 / 230 (7.39%)	23 / 456 (5.04%)	
occurrences (all)	20	34	
Respiratory, thoracic and mediastinal disorders			
Dysphonia			
subjects affected / exposed	12 / 230 (5.22%)	75 / 456 (16.45%)	
occurrences (all)	12	84	
Cough			
subjects affected / exposed	21 / 230 (9.13%)	39 / 456 (8.55%)	
occurrences (all)	24	50	
Dyspnoea			
subjects affected / exposed	22 / 230 (9.57%)	39 / 456 (8.55%)	
occurrences (all)	27	49	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 230 (5.22%)	26 / 456 (5.70%)	
occurrences (all)	12	26	
Investigations			
Weight decreased			
subjects affected / exposed	21 / 230 (9.13%)	58 / 456 (12.72%)	
occurrences (all)	21	82	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 230 (4.35%)	50 / 456 (10.96%)	
occurrences (all)	13	74	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 230 (3.48%)	49 / 456 (10.75%)	
occurrences (all)	10	74	
Blood bilirubin increased			
subjects affected / exposed	10 / 230 (4.35%)	33 / 456 (7.24%)	
occurrences (all)	14	43	
Blood thyroid stimulating hormone			

increased			
subjects affected / exposed	3 / 230 (1.30%)	32 / 456 (7.02%)	
occurrences (all)	3	35	
Platelet count decreased			
subjects affected / exposed	2 / 230 (0.87%)	28 / 456 (6.14%)	
occurrences (all)	2	38	
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 230 (4.35%)	24 / 456 (5.26%)	
occurrences (all)	11	29	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 230 (4.35%)	40 / 456 (8.77%)	
occurrences (all)	11	47	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	28 / 230 (12.17%)	38 / 456 (8.33%)	
occurrences (all)	39	55	
Thrombocytopenia			
subjects affected / exposed	3 / 230 (1.30%)	30 / 456 (6.58%)	
occurrences (all)	4	47	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	8 / 230 (3.48%)	35 / 456 (7.68%)	
occurrences (all)	9	45	
Stomatitis			
subjects affected / exposed	7 / 230 (3.04%)	67 / 456 (14.69%)	
occurrences (all)	8	108	
Constipation			
subjects affected / exposed	22 / 230 (9.57%)	75 / 456 (16.45%)	
occurrences (all)	25	82	
Abdominal pain			
subjects affected / exposed	36 / 230 (15.65%)	80 / 456 (17.54%)	
occurrences (all)	44	107	
Nausea			
subjects affected / exposed	43 / 230 (18.70%)	82 / 456 (17.98%)	
occurrences (all)	48	102	
Vomiting			

subjects affected / exposed	25 / 230 (10.87%)	67 / 456 (14.69%)	
occurrences (all)	32	81	
Diarrhoea			
subjects affected / exposed	24 / 230 (10.43%)	113 / 456 (24.78%)	
occurrences (all)	31	173	
Skin and subcutaneous tissue disorders			
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 230 (2.61%)	89 / 456 (19.52%)	
occurrences (all)	6	224	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	12 / 230 (5.22%)	81 / 456 (17.76%)	
occurrences (all)	25	167	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 230 (0.43%)	94 / 456 (20.61%)	
occurrences (all)	1	101	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	17 / 230 (7.39%)	48 / 456 (10.53%)	
occurrences (all)	24	61	
Pain in extremity			
subjects affected / exposed	6 / 230 (2.61%)	28 / 456 (6.14%)	
occurrences (all)	7	39	
Arthralgia			
subjects affected / exposed	10 / 230 (4.35%)	52 / 456 (11.40%)	
occurrences (all)	11	60	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	41 / 230 (17.83%)	127 / 456 (27.85%)	
occurrences (all)	48	178	
Hypokalaemia			
subjects affected / exposed	4 / 230 (1.74%)	29 / 456 (6.36%)	
occurrences (all)	6	36	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2020	Global Amendment 1: -Added language allowing subjects to continue receiving treatment following PD by RECIST v1.1 -Modified requirement for prior treatment with TAS-102 or regorafenib
30 October 2020	Global Amendment 2: -Increased the number of subjects to up to 687 and the planned number of sites from 100 sites to 140 sites -Provided country-level flexibility for molecular characterization of MSI/MMR status
16 March 2021	Global Amendment 3: -Added notes regarding temporary change of PK sampling, ECG collection, and ctDNA sample collection -Added specification to prohibit live vaccines during the study and for 3 months after the last dose of study drug(s) -Added specification that study drug should have been administered around the same time each day and that a missed dose could have been administered within 12 hours of usual administration time -Clarified statistical methods
24 June 2021	Global Amendment 4: -Removed instruction to avoid proton pump inhibitor drugs and H2 blockers -Increased the number of the planned study sites from 140 to 160 -Removed requirement for the collection of blood to evaluate ctDNA -Changed the protein level for which a 24-hour urine assessment was required
01 September 2022	Global Amendment 4 Addendum 1: Described the long-term extension plan, which was in place since the original protocol; visits and assessments to be performed for subjects continuing to receive fruquintinib were described to ensure their safety and clinical oversight.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported