Clinical trial results:
An Open-Label Phase 2 Study of Surufatinib in Patients with Neuroendocrine Tumors in Europe

Summary

EudraCT number	2020-006118-19
Trial protocol	FR DE NO IT ES
Global end of trial date	06 September 2024

Results information

Result version number	v1 (current)
This version publication date	31 August 2025
First version publication date	31 August 2025

Trial information

Trial identification

Sponsor protocol code	2020-012-00EU1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04579679
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	HUTCHMED Limited
Sponsor organisation address	Building 4, 720 Cailun Road China (Shanghai) Pilot Free Trade Zone, Shanghai, China, 201203
Public contact	Nick Lawn, HUTCHMED International Corporation, +44 7826 422448, nickl@hutch-med.com
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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	15 October 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 September 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the anti-tumor activity of surufatinib in patients with low- to intermediate-grade (Grade 1 or Grade 2), well-differentiated neuroendocrine tumors (NET).

Protection of trial subjects:

This study was conducted in accordance with the protocol, the ethical principles derived from international guidelines, including the Declaration of Helsinki and/or all relevant federal regulations in compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Harmonized Tripartite Guideline, Council for International Organizations of Medical Sciences International Ethical Guidelines, Good Clinical Practice guidelines, and according to the appropriate regulatory requirements in the countries where the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 August 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 6
Worldwide total number of subjects	78
EEA total number of subjects	69

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)	38
From 65 to 84 years	40
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 2, open-label, multi-center study was conducted in patients with locally advanced or metastatic low to intermediate grade (Grade 1 or Grade 2), well-differentiated NETs. The study was terminated early based on strategic re-evaluation of clinical development program for surufatinib and not due to any safety concerns.

Pre-assignment

Screening details:

The study enrolled patients in 4 cohorts of varying NETs, as follows:
• Cohort A - NET of lung origin (NET, lung)
• Cohort B - NET of small bowel origin (NET, small bowel)
• Cohort C - NET of non-small bowel, non-pancreas, and non-lung origin (NET, other)
• Cohort D - NET of any origin (NET, any).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A (NET, Lung)

Arm description:

Patients with NET of lung origin received surufatinib 300 milligrams (mg) orally once daily (QD) in treatment cycles of 28 days starting on Cycle (C)1 Day (D)1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Arm type	Experimental
Investigational medicinal product name	Surufatinib
Investigational medicinal product code	
Other name	HMPL-012
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Surufatinib 300 mg was administered orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Arm title	Cohort B (NET, Small Bowel)

Arm description:

Patients with NET of small bowel origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Arm type	Experimental
Investigational medicinal product name	Surufatinib
Investigational medicinal product code	
Other name	HMPL-012
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Surufatinib 300 mg was administered orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Arm title	Cohort C (NET, Other)

Arm description:

Patients with NET of non-small bowel, non-pancreas, and non-lung origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Arm type	Experimental
Investigational medicinal product name	Surufatinib
Investigational medicinal product code	
Other name	HMPL-012
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Surufatinib 300 mg was administered orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Arm title	Cohort D (NET, Any)

Arm description:

Patients with NET of any origin received a single dose of drug cocktail (midazolam 2.5 mg, fexofenadine 30 mg and rosuvastatin 10 mg) on Day -2 followed by surufatinib 300 mg orally QD from C1D1 to C1D14. On C1D15, a single dose of surufatinib 300 mg and a single dose of drug cocktail as above was administered. Patients received surufatinib 300 mg orally QD from C1D16 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Arm type	Experimental
Investigational medicinal product name	Surufatinib
Investigational medicinal product code	
Other name	HMPL-012
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Surufatinib 300 mg was administered orally QD as mentioned in the protocol.

Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

Midazolam 2.5 mg was administered as a part of drug cocktail as per protocol to patients in Cohort D.

Investigational medicinal product name	Fexofenadine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Fexofenadine 30 mg was administered as a part of drug cocktail as per protocol to patients in Cohort D.

Investigational medicinal product name	Rosuvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Rosuvastatin 10 mg was administered as a part of drug cocktail as per protocol to patients in Cohort D.

Number of subjects in period 1	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)
Started	20	32	20
Completed	0	1	0
Not completed	20	31	20
Consent withdrawn by subject	1	1	2
Physician decision	-	-	1
Adverse event, non-fatal	-	4	-
Death	2	2	2
New Antitumor Therapy	6	4	7
Study terminated by sponsor	2	7	1
Disease Progression	9	13	7

Number of subjects in period 1	Cohort D (NET, Any)
Started	6
Completed	2
Not completed	4
Consent withdrawn by subject	4
Physician decision	-
Adverse event, non-fatal	-
Death	-
New Antitumor Therapy	-
Study terminated by sponsor	-
Disease Progression	-

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A (NET, Lung)
Reporting group description:	
Patients with NET of lung origin received surufatinib 300 milligrams (mg) orally once daily (QD) in treatment cycles of 28 days starting on Cycle (C)1 Day (D)1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	
Reporting group title	Cohort B (NET, Small Bowel)
Reporting group description:	
Patients with NET of small bowel origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	
Reporting group title	Cohort C (NET, Other)
Reporting group description:	
Patients with NET of non-small bowel, non-pancreas, and non-lung origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	
Reporting group title	Cohort D (NET, Any)
Reporting group description:	
Patients with NET of any origin received a single dose of drug cocktail (midazolam 2.5 mg, fexofenadine 30 mg and rosuvastatin 10 mg) on Day -2 followed by surufatinib 300 mg orally QD from C1D1 to C1D14. On C1D15, a single dose of surufatinib 300 mg and a single dose of drug cocktail as above was administered. Patients received surufatinib 300 mg orally QD from C1D16 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	

Reporting group values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)
Number of subjects	20	32	20
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.5	62.1	57.3
standard deviation	± 12.77	± 10.44	± 15.52
Gender categorical Units: Subjects			
Female	7	20	9
Male	13	12	11
Race Units: Subjects			
American Indian or Alaska Native	0	1	0
Black or African American	0	0	0
White	15	28	13
Not Reported	4	1	7
Other	0	1	0
Missing	1	1	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	3	0
Not Hispanic or Latino	15	26	13

Unknown or Not Reported	5	3	7

Reporting group values	Cohort D (NET, Any)	Total	
Number of subjects	6	78	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.5		
standard deviation	± 7.40	-	
Gender categorical Units: Subjects			
Female	4	40	
Male	2	38	
Race Units: Subjects			
American Indian or Alaska Native	0	1	
Black or African American	3	3	
White	3	59	
Not Reported	0	12	
Other	0	1	
Missing	0	2	
Ethnicity Units: Subjects			
Hispanic or Latino	0	3	
Not Hispanic or Latino	6	60	
Unknown or Not Reported	0	15	

End points

End points reporting groups

Reporting group title	Cohort A (NET, Lung)
Reporting group description:	
Patients with NET of lung origin received surufatinib 300 milligrams (mg) orally once daily (QD) in treatment cycles of 28 days starting on Cycle (C)1 Day (D)1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	

Reporting group title	Cohort B (NET, Small Bowel)
Reporting group description:	
Patients with NET of small bowel origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	

Reporting group title	Cohort C (NET, Other)
Reporting group description:	
Patients with NET of non-small bowel, non-pancreas, and non-lung origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	

Reporting group title	Cohort D (NET, Any)
Reporting group description:	
Patients with NET of any origin received a single dose of drug cocktail (midazolam 2.5 mg, fexofenadine 30 mg and rosuvastatin 10 mg) on Day -2 followed by surufatinib 300 mg orally QD from C1D1 to C1D14. On C1D15, a single dose of surufatinib 300 mg and a single dose of drug cocktail as above was administered. Patients received surufatinib 300 mg orally QD from C1D16 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.	

Primary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)[1]
End point description:	
The DCR was defined as the percentage of patients who achieved a best overall response (BOR) of complete response (CR), partial response (PR) or stable disease (SD) as determined by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version (v)1.1. The CR was defined as disappearance of all target lesions. The PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum on study. The efficacy analysis set included all patients who received at least 1 dose of surufatinib and had at least 1 post-baseline tumor assessment.	
End point type	Primary
End point timeframe:	
RECIST assessments performed at screening (within 28 days before start of study drug), every 8 weeks for the first 24 weeks from C1D1, then every 12 weeks thereafter until the occurrence of disease progression, up to approximately 36 months	

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: As the endpoint is descriptive in nature, no statistical analysis is presented.

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	31	19	5
Units: percentage of participants				
number (confidence interval 95%)	95.0 (75.1 to 99.9)	90.3 (74.2 to 98.0)	89.5 (66.9 to 98.7)	100 (47.8 to 100)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Surufatinib

End point title	Plasma Concentrations of Surufatinib

End point description:

Blood samples were collected at specified timepoints to obtain plasma concentrations of surufatinib at steady state on Cycle 1 Day 15. The pharmacokinetic (PK) analysis set included all patients who received at least 1 dose of the study drug and had at least 1 measurable plasma concentration data point for at least 1 PK analyte without protocol violations or events with potential to affect the PK concentration. Here, n=only those participants with data collected at specified timepoints and 99999= no data as there were no participants analyzed for that timepoint for that cohort.

End point type	Secondary

End point timeframe:

Cohorts A, B and C: Pre-dose and 1, 2, 3, 4 hours post-dose on Cycle 1 Day 15; Cohort D: Pre-dose and 30 minutes, 1, 2, 3, 4, 5, 6, 8 and 10 hours post-dose on Cycle 1 Day 15

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17	29	18	6
Units: nanogram/milliliter				
geometric mean (geometric coefficient of variation)				
Pre-dose (n=17,25,18,6)	73.123 (± 70.1)	57.593 (± 136.8)	49.258 (± 54.7)	28.913 (± 130.5)
30 minutes post-dose (n=0,0,0,6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	50.439 (± 190.5)
1 hour post-dose (n=17,29,15,6)	130.456 (± 118.3)	96.163 (± 115.2)	101.464 (± 125.6)	129.719 (± 303.6)
2 hours post-dose (n=17,27,18,6)	234.498 (± 122.1)	174.799 (± 138.1)	194.654 (± 80.5)	321.942 (± 99.9)
3 hours post-dose (n=17,29,18,6)	287.237 (± 95.0)	250.348 (± 101.8)	245.379 (± 55.1)	477.653 (± 118.6)
4 hours post-dose (n=17,28,17,6)	293.236 (± 85.6)	268.619 (± 65.9)	232.657 (± 42.6)	389.597 (± 102.8)
5 hours post-dose (n=0,0,0,6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	357.045 (± 105.4)
6 hours post-dose (n=0,0,0,6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	280.691 (± 105.2)
8 hours post-dose (n=0,0,0,6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	202.345 (± 102.7)
10 hours post-dose (n=0,0,0,4)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	174.079 (± 84.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Potentially Clinically Significant Corrected QT Interval (QTc) During Treatment

End point title	Number of Patients With Potentially Clinically Significant Corrected QT Interval (QTc) During Treatment

End point description:

The QT interval data was corrected for heart rate using 2 correction methods (Fridericia – QTcF and Bazett – QTcB). The treatment period was defined as the period from first administration of study drug up 30 days after last administration. The safety analysis set included all patients who received at least 1 dose of surufatinib. Here, n= only those patients with data collected for specified categories. msec=milliseconds, IFB=increase from baseline.

End point type	Secondary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 days after last dose of study drug, approximately 33 months

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	31	19	6
Units: participants				
QTcF: >450 msec to <=480 msec (n=19,31,18,6)	0	2	0	2
QTcF: >480 msec to <=500 msec (n=19,31,18,6)	0	4	1	0
QTcF: >500 msec (n=19,31,18,6)	0	0	0	1
QTcF: IFB >30 msec to <=60 msec (n=19,31,18,6)	4	2	1	1
QTcF: IFB >60 msec (n=19,31,18,6)	0	2	0	1
QTcB: >450 msec to <=480 msec (n=19,31,19,6)	3	6	3	4
QTcB: >480 msec to <=500 msec (n=19,31,19,6)	0	1	0	1
QTcB: >500 msec (n=19,31,19,6)	0	1	1	1
QTcB: IFB >30 msec to <=60 msec (n=19,31,19,6)	2	7	4	1
QTcB: IFB >60 msec (n=19,31,19,6)	1	2	0	1

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

The ORR was defined as the percentage of patients with a BOR of CR or PR as determined by the Investigator using RECIST v1.1. The CR was defined as disappearance of all target lesions. The PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. The efficacy analysis set included all patients who received at least 1 dose of surufatinib and had at least 1 post-baseline tumor assessment.

End point type	Secondary

End point timeframe:

RECIST assessments performed at screening (within 28 days before start of study drug), every 8 weeks for the first 24 weeks from C1D1, then every 12 weeks thereafter until the occurrence of disease progression, up to approximately 36 months

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	31	19	5
Units: percentage of participants				
number (confidence interval 95%)	15.0 (3.2 to 37.9)	16.1 (5.5 to 33.7)	5.3 (0.1 to 26.0)	20.0 (0.5 to 71.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

The TTR was defined as the time from the start of study drug until the date of first documented objective response, either CR or PR (whichever was recorded first) according to RECIST v.1.1 for responders only. The CR was defined as disappearance of all target lesions. The PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. The efficacy analysis set included all patients who received at least 1 dose of surufatinib and had at least 1 post-baseline tumor assessment. Only those patients who achieved CR/PR (responders) were included in the analysis.

End point type	Secondary

End point timeframe:

RECIST assessments performed at screening (within 28 days before start of study drug), every 8 weeks for the first 24 weeks from C1D1, then every 12 weeks thereafter until the occurrence of disease progression, up to approximately 36 months

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	1	1
Units: months				
median (full range (min-max))	2.1 (1.6 to 5.3)	3.7 (1.8 to 14.2)	11.1 (11.1 to 11.1)	13.6 (13.6 to 13.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

The DoR was defined as the time from the first time that the objective response reached CR or PR, whichever came first (and later confirmed), until the occurrence of PD or death.CR was defined as disappearance of all target lesions.PR was defined as at least 30% decrease in sum of diameters of target lesions, taking as reference baseline sum of diameters. PD was defined as at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study (nadir), including baseline. In addition to the relative increase of 20%, sum must also demonstrate an absolute increase of at least 5 millimeters. Appearance of 1 or more new lesions was also considered progression. Analysis was performed on efficacy analysis set. Only patients with PR or CR (responders) were included in the analysis. 55555=not estimable due to insufficient number of patients with events at study closure;-22222 and 22222=cannot be calculated for 1 patient.

End point type	Secondary

End point timeframe:

RECIST assessments performed at screening (within 28 days before start of study drug), every 8 weeks for the first 24 weeks from C1D1, then every 12 weeks thereafter until the occurrence of disease progression, up to approximately 36 months

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	5	1	1
Units: months				
median (confidence interval 95%)	16.9 (8.6 to 55555)	15.4 (3.7 to 55555)	5.6 (-22222 to 22222)	55555 (55555 to 55555)

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

The PFS was defined as the time from the start of study drug until the first objective PD as defined by RECIST v1.1 or death, whichever came first. The 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 (nadir), including baseline.

In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimeters. The appearance of 1 or more new lesions was also considered progression. The safety analysis set included all patients who received at least 1 dose of surufatinib. 55555=not estimable due to insufficient number of patients with events at study closure.

End point type	Secondary

End point timeframe:

RECIST assessments performed at screening (within 28 days before start of study drug), every 8 weeks for the first 24 weeks from C1D1, then every 12 weeks thereafter until the occurrence of disease progression, up to approximately 36 months

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	32	20	6
Units: months				
median (confidence interval 95%)	10.2 (5.4 to 16.6)	19.2 (8.3 to 55555)	11.4 (5.7 to 16.7)	9.8 (7.2 to 55555)

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort D: Geometric Least Squares (LS) Mean Ratio of Cytochrome P450 (CYP3A4), P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) Substrates at Cycle 1 Day 15 to Baseline

End point title	Cohort D: Geometric Least Squares (LS) Mean Ratio of Cytochrome P450 (CYP3A4), P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) Substrates at Cycle 1 Day 15 to Baseline[2]

End point description:

Participants were administered midazolam, fexofenadine and rosuvastatin (as part of the drug cocktail) as a single dose on Day -2 (without surufatinib) and on Cycle 1 Day 15 (with surufatinib). Separate blood samples were collected for measurement of plasma concentrations of each probe substrate and surufatinib. Probe substrate of midazolam was CYP3A4, fexofenadine was P-gp and rosuvastatin was BCRP. Ratio of LS Mean for maximum plasma concentration (Cmax), area under the plasma concentration-time curve from time 0 to time of last measurable concentration (AUC0-t) and area under the plasma concentration-time curve from time 0 to infinity (AUC0-inf) are presented as Cycle 1 Day 15/Day -2. The PK evaluable population included all patients who received at least 1 dose of the study drug and had sufficient concentration data to derive at least 1 PK parameter.

End point type	Secondary

End point timeframe:

Baseline (Day -2) and Cycle 1 Day 15

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only Cohort D is evaluated for this endpoint.

End point values	Cohort D (NET, Any)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Ratio of geometric LS mean				
number (confidence interval 90%)				
Midazolam (CYP3A4 substrate), Cmax	1.69 (1.20 to 2.39)			
Midazolam (CYP3A4 substrate), AUC0-t	1.70 (1.14 to 2.52)			
Midazolam (CYP3A4 substrate), AUC0-inf	1.71 (1.16 to 2.53)			
Fexofenadine (P-gp substrate), Cmax	2.03 (1.51 to 2.75)			
Fexofenadine (P-gp substrate), AUC0-t	2.12 (1.65 to 2.73)			
Fexofenadine (P-gp substrate), AUC0-inf	2.14 (1.64 to 2.78)			
Rosuvastatin (BCRP substrate), Cmax	2.23 (1.59 to 3.14)			
Rosuvastatin (BCRP substrate), AUC0-t	2.13 (1.31 to 3.48)			
Rosuvastatin (BCRP substrate), AUC0-inf	2.23 (1.23 to 4.01)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

An AE is any untoward medical occurrence in a clinical study patient temporally associated with the use of a study drug, whether or not considered related to the drug. An SAE was an AE that resulted in any of the following outcomes: death; was life threatening; required inpatient hospitalization or prolongation of existing hospitalization; resulted persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; a congenital anomaly/birth defect or was any important medical event. TEAEs were defined as any AEs that started or worsened in severity on or after the first administration date of study drug and no later than 30 (+7) days after the last administration date of study drug or initiation of new anti-tumor therapy (whichever occurred first). The safety analysis set included all patients who received at least 1 dose of surufatinib.

End point type	Secondary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 days after last dose of study drug, approximately 33 months

End point values	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)	Cohort D (NET, Any)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	32	20	6
Units: participants				
TEAEs	20	32	20	6
TESAEs	4	12	8	2

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the first dose of study drug (Day 1) up to 30 days after last dose of study drug, approximately 33 months. Deaths were collected from screening (Day -28) up to end of follow-up, approximately 36 months

Adverse event reporting additional description:

The safety analysis set included all patients who received at least 1 dose of surufatinib.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Cohort A (NET, Lung)

Reporting group description:

Patients with NET of lung origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Reporting group title	Cohort B (NET, Small Bowel)

Reporting group description:

Patients with NET of small bowel origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Reporting group title	Cohort C (NET, Other)

Reporting group description:

Patients with NET of non-small bowel, non-pancreas, and non-lung origin received surufatinib 300 mg orally QD in treatment cycles of 28 days starting on C1D1 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Reporting group title	Cohort D (NET, Any)

Reporting group description:

Patients with NET of any origin received a single dose of drug cocktail (midazolam 2.5 mg, fexofenadine 30 mg and rosuvastatin 10 mg) on Day -2 followed by surufatinib 300 mg orally QD from C1D1 to C1D14. On C1D15, a single dose of surufatinib 300 mg and a single dose of drug cocktail as above was administered. Patients received surufatinib 300 mg orally QD from C1D16 until disease progression, death, unacceptable toxicity, withdrawal of consent or lost to follow-up.

Serious adverse events	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)	12 / 32 (37.50%)	8 / 20 (40.00%)
number of deaths (all causes)	2	2	2
number of deaths resulting from adverse events	0	1	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Malignant neoplasm progression			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Tumour haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Multisystem inflammatory syndrome			

subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac function test abnormal			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary obstruction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic function abnormal			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal artery dissection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort D (NET, Any)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant neoplasm progression			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour haemorrhage			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive emergency			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Multisystem inflammatory syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthmatic crisis			

subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood bilirubin increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood creatinine increased				
subjects affected / exposed	1 / 6 (16.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac function test abnormal				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Atrial fibrillation				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrioventricular block				
subjects affected / exposed	0 / 6 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac failure			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Large intestinal obstruction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pancreatitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary obstruction			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic function abnormal			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal artery dissection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal infarct			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Failure to thrive			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort A (NET, Lung)	Cohort B (NET, Small Bowel)	Cohort C (NET, Other)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)	32 / 32 (100.00%)	20 / 20 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	14 / 20 (70.00%)	16 / 32 (50.00%)	15 / 20 (75.00%)
occurrences (all)	32	41	35
Flushing			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	2 / 20 (10.00%)
occurrences (all)	3	2	2
Hypotension			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	0	3	1
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	14 / 20 (70.00%)	20 / 32 (62.50%)	13 / 20 (65.00%)
occurrences (all)	49	47	22
Pyrexia			
subjects affected / exposed	6 / 20 (30.00%)	7 / 32 (21.88%)	4 / 20 (20.00%)
occurrences (all)	11	12	4
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	10 / 32 (31.25%)	1 / 20 (5.00%)
occurrences (all)	1	17	6
Oedema peripheral			
subjects affected / exposed	3 / 20 (15.00%)	7 / 32 (21.88%)	3 / 20 (15.00%)
occurrences (all)	4	9	3
Mucosal inflammation			
subjects affected / exposed	2 / 20 (10.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	3	3	1
Influenza like illness			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Oedema			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Peripheral swelling			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Genital hypoaesthesia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Heavy menstrual bleeding			

subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Pelvic pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Vaginal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 20 (30.00%)	1 / 32 (3.13%)	4 / 20 (20.00%)
occurrences (all)	9	2	4
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)	3 / 32 (9.38%)	1 / 20 (5.00%)
occurrences (all)	1	4	1
Epistaxis			
subjects affected / exposed	2 / 20 (10.00%)	2 / 32 (6.25%)	2 / 20 (10.00%)
occurrences (all)	4	2	2
Dyspnoea exertional			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Haemoptysis			
subjects affected / exposed	2 / 20 (10.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	3	2	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	5 / 32 (15.63%)	0 / 20 (0.00%)
occurrences (all)	0	5	0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 20 (15.00%)	8 / 32 (25.00%)	2 / 20 (10.00%)
occurrences (all)	6	14	3
Blood bilirubin increased			
subjects affected / exposed	5 / 20 (25.00%)	2 / 32 (6.25%)	4 / 20 (20.00%)
occurrences (all)	12	5	11
Alanine aminotransferase increased			

subjects affected / exposed	2 / 20 (10.00%)	6 / 32 (18.75%)	2 / 20 (10.00%)
occurrences (all)	2	13	3
Weight decreased			
subjects affected / exposed	5 / 20 (25.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	5	2	0
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 20 (15.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	5	4	0
Blood creatinine increased			
subjects affected / exposed	3 / 20 (15.00%)	1 / 32 (3.13%)	2 / 20 (10.00%)
occurrences (all)	3	2	4
Platelet count decreased			
subjects affected / exposed	1 / 20 (5.00%)	3 / 32 (9.38%)	0 / 20 (0.00%)
occurrences (all)	1	3	0
Amylase increased			
subjects affected / exposed	3 / 20 (15.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	3	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	2	4	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Bilirubin conjugated increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Troponin increased			

subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Fall			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1
Head injury			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Muscle rupture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Tooth fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Sunburn			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Joint dislocation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Foot fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Radius fracture			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Limb injury			

subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 20 (10.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	2	0	0
Tachycardia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 20 (30.00%)	4 / 32 (12.50%)	0 / 20 (0.00%)
occurrences (all)	8	5	0
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	3 / 32 (9.38%)	1 / 20 (5.00%)
occurrences (all)	1	3	1
Sciatica			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	4 / 20 (20.00%)
occurrences (all)	0	1	7
Dysgeusia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	1	4	0
Tremor			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	0	3	2
Hypoaesthesia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 20 (10.00%)	5 / 32 (15.63%)	3 / 20 (15.00%)
occurrences (all)	2	8	8
Leukocytosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Thrombocytopenia			

subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 20 (5.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	1	1	0
Vertigo			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Acute vestibular syndrome			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 20 (55.00%)	22 / 32 (68.75%)	13 / 20 (65.00%)
occurrences (all)	20	82	24
Nausea			
subjects affected / exposed	5 / 20 (25.00%)	10 / 32 (31.25%)	4 / 20 (20.00%)
occurrences (all)	7	30	6
Abdominal pain			
subjects affected / exposed	2 / 20 (10.00%)	11 / 32 (34.38%)	3 / 20 (15.00%)
occurrences (all)	4	23	3
Vomiting			
subjects affected / exposed	6 / 20 (30.00%)	5 / 32 (15.63%)	4 / 20 (20.00%)
occurrences (all)	8	19	6
Constipation			
subjects affected / exposed	2 / 20 (10.00%)	4 / 32 (12.50%)	5 / 20 (25.00%)
occurrences (all)	3	4	6
Abdominal pain upper			
subjects affected / exposed	2 / 20 (10.00%)	3 / 32 (9.38%)	3 / 20 (15.00%)
occurrences (all)	2	3	3
Flatulence			

subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	3 / 20 (15.00%)
occurrences (all)	0	3	3
Stomatitis			
subjects affected / exposed	2 / 20 (10.00%)	1 / 32 (3.13%)	2 / 20 (10.00%)
occurrences (all)	4	1	2
Dry mouth			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	1	5	0
Dyspepsia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	2	1	0
Abdominal distension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Abdominal pain lower			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	1	3	0
Hypertransaminasaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 20 (5.00%)	3 / 32 (9.38%)	2 / 20 (10.00%)
occurrences (all)	1	5	2
Rash			
subjects affected / exposed	0 / 20 (0.00%)	4 / 32 (12.50%)	0 / 20 (0.00%)
occurrences (all)	0	4	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	1	2	1
Pruritus			

subjects affected / exposed	0 / 20 (0.00%)	3 / 32 (9.38%)	1 / 20 (5.00%)
occurrences (all)	0	5	1
Alopecia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Rash macular			
subjects affected / exposed	0 / 20 (0.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Skin hyperpigmentation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	7 / 20 (35.00%)	7 / 32 (21.88%)	6 / 20 (30.00%)
occurrences (all)	20	15	10
Haematuria			
subjects affected / exposed	3 / 20 (15.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	3	4	1
Acute kidney injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	2 / 20 (10.00%)
occurrences (all)	0	1	2
Urinary incontinence			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 20 (10.00%)	8 / 32 (25.00%)	0 / 20 (0.00%)
occurrences (all)	4	8	0
Hyperthyroidism			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	0	1	0
Thyroid pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	5 / 20 (25.00%)	9 / 32 (28.13%)	4 / 20 (20.00%)
occurrences (all)	6	17	8
Back pain			
subjects affected / exposed	5 / 20 (25.00%)	4 / 32 (12.50%)	4 / 20 (20.00%)
occurrences (all)	6	7	6
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)	3 / 32 (9.38%)	1 / 20 (5.00%)
occurrences (all)	2	3	1
Myalgia			
subjects affected / exposed	2 / 20 (10.00%)	1 / 32 (3.13%)	2 / 20 (10.00%)
occurrences (all)	3	2	4
Muscle spasms			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	4 / 20 (20.00%)
occurrences (all)	0	0	6
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Flank pain			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	4	2	0
Torticollis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	3
Infections and infestations			
COVID-19			
subjects affected / exposed	3 / 20 (15.00%)	11 / 32 (34.38%)	0 / 20 (0.00%)
occurrences (all)	3	16	0
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	5 / 32 (15.63%)	3 / 20 (15.00%)
occurrences (all)	0	5	4
Nasopharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	3 / 32 (9.38%)	1 / 20 (5.00%)
occurrences (all)	2	3	1
Influenza			

subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	0 / 20 (0.00%)
occurrences (all)	2	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 20 (25.00%)	6 / 32 (18.75%)	7 / 20 (35.00%)
occurrences (all)	7	20	14
Hyperkalaemia			
subjects affected / exposed	1 / 20 (5.00%)	3 / 32 (9.38%)	2 / 20 (10.00%)
occurrences (all)	1	3	2
Hypomagnesaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Hyperuricaemia			
subjects affected / exposed	1 / 20 (5.00%)	2 / 32 (6.25%)	1 / 20 (5.00%)
occurrences (all)	1	3	1
Hypertriglyceridaemia			
subjects affected / exposed	0 / 20 (0.00%)	3 / 32 (9.38%)	0 / 20 (0.00%)
occurrences (all)	0	9	0
Hypocalcaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 32 (3.13%)	3 / 20 (15.00%)
occurrences (all)	0	1	3
Hypophosphataemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 32 (3.13%)	2 / 20 (10.00%)
occurrences (all)	1	1	2
Hypokalaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 20 (5.00%)	1 / 32 (3.13%)	0 / 20 (0.00%)
occurrences (all)	1	2	0
Dehydration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 32 (0.00%)	0 / 20 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort D (NET, Any)		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	6 / 6 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Flushing			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	4		
Oedema peripheral			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Mucosal inflammation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Non-cardiac chest pain			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Oedema			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Peripheral swelling			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Erectile dysfunction			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Genital hypoaesthesia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Heavy menstrual bleeding			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pelvic pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vaginal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dyspnoea exertional			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Amylase increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Bilirubin conjugated increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Troponin increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Head injury			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Muscle rupture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Tooth fracture			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Post procedural haemorrhage			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Sunburn subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Joint dislocation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Foot fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Radius fracture subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Limb injury subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Tachycardia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Dizziness subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Sciatica subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		
Dysgeusia			

subjects affected / exposed occurrences (all) Tremor subjects affected / exposed occurrences (all) Hypoaesthesia subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukocytosis subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 2 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1		
Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all) Vertigo subjects affected / exposed occurrences (all) Acute vestibular syndrome subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0		
Eye disorders Diplopia subjects affected / exposed occurrences (all)	 0 / 6 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea	 2 / 6 (33.33%) 4		

subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Constipation			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Abdominal distension			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Abdominal pain lower			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		

Hypertransaminasaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash macular			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin hyperpigmentation			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	4		
Haematuria			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Urinary incontinence			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hyperthyroidism			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Thyroid pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Torticollis			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Influenza			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	3 / 6 (50.00%)		
occurrences (all)	3		
Hyperuricaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypertriglyceridaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypophosphataemia			

subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Hypokalaemia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	4		
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2021	Revision of eligibility criteria. Minor clarifications.
23 June 2021	Added clarifications per health authority request. Removed proton pump inhibitors from the list of prohibited therapies and instructions to avoid proton pump inhibitors. Clarified the screening pregnancy test was to be completed within 7 days before the start of surufatinib treatment. Removed C1D2 visit; added screening visit range Day -7 to 1. Added provision to allow enrollment of additional patients. Minor clarifications and modifications for consistency.
12 August 2021	Added clarifications about enrollment. Addressed Ethic Committee comments. Minor clarifications and addition of United States sites.
01 March 2022	Language was updated to reflect company name change and throughout the document for clarity. Updated total enrollment.
05 December 2022	Language updated for clarity throughout the document. The addition of the time window was intended to provide flexibility in obtaining patient assessments relative to dosing.

Notes:

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.

Based upon the strategic reevaluation of the clinical development program for surufatinib in Europe and the US, the study was terminated. The termination was not based on any concern for patient safety or efficacy relative to surufatinib treatment.

Notes: