Clinical trial results:
AN OPEN-LABEL, MULTICENTER PHASE 1/2 STUDY OF SURUFATINIB IN COMBINATION WITH GEMCITABINE IN PEDIATRIC, ADOLESCENT, AND YOUNG ADULT PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

Summary

EudraCT number	2021-003602-41
Trial protocol	IT DE ES DK
Global end of trial date	25 April 2023

Results information

Result version number	v1 (current)
This version publication date	11 November 2023
First version publication date	11 November 2023

Trial information

Trial identification

Sponsor protocol code	2020-012-GLOB2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05093322
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	Mark Woods, HUTCHMED Limited, 0044 7467 414995, markw@hutch-med.com
Scientific contact	Marjo Hahka-Kemppinen, HUTCHMED Limited, +358 40 842 5802, marjoh@hutch-med.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002750-PIP01-19
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	25 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine the maximum tolerated dose and/or recommended Phase 2 dose of surufatinib, and to evaluate the safety and tolerability of surufatinib in combination with gemcitabine in pediatric patients with recurrent or refractory solid tumors or lymphoma.

Protection of trial subjects:

The study was conducted in accordance with the protocol, consensus, and 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 Harmonization Good Clinical Practice guidelines, and applicable regulations and guidelines governing clinical study conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	13
EEA total number of subjects	4

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)	5
Adolescents (12-17 years)	7
Adults (18-64 years)	1
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This Phase 1/2 open-label study was conducted in pediatric, adolescent, and young adult patients with recurrent or refractory solid tumors at 8 study sites.

Pre-assignment

Screening details:

This study consisted of a screening period (up to 28 days), followed by a treatment phase (Cycle 1: 35 days and subsequent cycles: 21 days) and safety follow-up period (up to 30 days). A total of 13 patients were enrolled in this study.

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	Dose Level 1

Arm description:

Participants received surufatinib 120 milligram/meter square (mg/m^2) oral capsule once daily (QD) as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose intravenous (IV) infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until progressive disease (PD), unacceptable toxicity, or death; whichever came first.

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

Dosage and administration details:

Surufatinib 120 mg/m^2 oral capsule was administered QD in all treatment cycles until PD, unacceptable toxicity, or death; whichever came first.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1000 mg/m^2/dose IV infusion was administered over a period of 90 minutes on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until PD, unacceptable toxicity, or death; whichever came first.

Arm title	Dose Level 2

Arm description:

Participants received surufatinib 160 mg/m^2 oral capsule QD as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose IV infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until PD, unacceptable toxicity, or death; whichever came first.

Arm type	Experimental

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

Dosage and administration details:

Surufatinib 160 mg/m^2 oral capsule was administered QD in all treatment cycles until PD, unacceptable toxicity, or death; whichever came first.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Gemcitabine 1000 mg/m^2/dose IV infusion was administered over a period of 90 minutes on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until PD, unacceptable toxicity, or death; whichever came first.

Number of subjects in period 1	Dose Level 1	Dose Level 2
Started	10	3
Completed	0	0
Not completed	10	3
Death	6	2
Unspecified	4	1

Baseline characteristics

Reporting groups	
Reporting group title	Dose Level 1
Reporting group description:	
Participants received surufatinib 120 milligram/meter square (mg/m^2) oral capsule once daily (QD) as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose intravenous (IV) infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until progressive disease (PD), unacceptable toxicity, or death; whichever came first.	
Reporting group title	Dose Level 2
Reporting group description:	
Participants received surufatinib 160 mg/m^2 oral capsule QD as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose IV infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until PD, unacceptable toxicity, or death; whichever came first.	

Reporting group values	Dose Level 1	Dose Level 2	Total
Number of subjects	10	3	13
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	11.8	13.7	
standard deviation	± 5.55	± 2.89	-
Gender categorical Units: Subjects			
Female	4	1	5
Male	6	2	8
Ethnicity Units: Subjects			
Hispanic or Latino	1	2	3
Not Hispanic or Latino	9	1	10
Race Units: Subjects			
Black or African American	2	0	2
White	7	2	9
Not Reported	1	1	2

End points

End points reporting groups

Reporting group title	Dose Level 1

Reporting group description:

Participants received surufatinib 120 milligram/meter square (mg/m^2) oral capsule once daily (QD) as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose intravenous (IV) infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until progressive disease (PD), unacceptable toxicity, or death; whichever came first.

Reporting group title	Dose Level 2

Reporting group description:

Participants received surufatinib 160 mg/m^2 oral capsule QD as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose IV infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until PD, unacceptable toxicity, or death; whichever came first.

Primary: Number of Patients With Dose-Limiting Toxicities (DLT)

End point title	Number of Patients With Dose-Limiting Toxicities (DLT)[1]

End point description:

A DLT was defined as any of following events that were attributable to study treatment (at least possibly related). Adverse events (AE) were graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.
• Any Grade 3 or greater nonhematological toxicity.
• Grade 3 liver enzyme elevation.
• Cases of Hy’s law.
• Any Grade 2 nonhematological toxicity that persisted for >= 7 days.
• Any Grade 4 hypertension.
• Grade 3 corrected QT interval prolongation > 500 millisecond.
• Grade 4 thrombocytopenia for > 7 days.
• Grade 3 thrombocytopenia with clinically significant bleeding.
• Grade 4 neutropenia that lasted for > 7 days.
• Myelosuppression that caused a delay of > 7 days in the start of Cycle 2.
DLT evaluable set included all patients enrolled in dose escalation phase of study who received at least 80% of surufatinib dose and both doses of gemcitabine during DLT evaluation period or who discontinued treatment due to a DLT.

End point type	Primary

End point timeframe:

From the first dose of study drug (Day 1) up to Day 35 of Cycle 1.

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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	3		
Units: patients	0	2		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients With Treatment Emergent Adverse Events (TEAEs) by Severity

End point title	Number of Patients With Treatment Emergent Adverse Events (TEAEs) by Severity[2]

End point description:

The AEs were graded using the NCI CTCAE version 5.0. The CTCAE displays Grades 1 through 5 where, Grade 1= mild, Grade 2= moderate, Grade 3= Severe, Grade 4= life-threatening consequences and Grade 5= death. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Primary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 + 7 days after the last dose of study drug, approximately 19 weeks

Notes:

[2] - 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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: patients				
Grade 1	0	0		
Grade 2	1	1		
Grade 3	4	2		
Grade 4	3	0		
Grade 5	2	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients with Clinically Significant Physical Examination Abnormalities

End point title	Number of Patients with Clinically Significant Physical Examination Abnormalities[3]

End point description:

Physical examination included patient height, weight, and general condition, as well as an examination of the head, heart, chest (including the lungs), abdomen, extremities, skin, lymph nodes, nervous system, and additional areas/systems as clinically indicated. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Primary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 + 7 days after the last dose of study drug, approximately 19 weeks

Notes:

[3] - 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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: patients	6	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients with Clinically Significant Vital Signs Abnormalities

End point title	Number of Patients with Clinically Significant Vital Signs Abnormalities[4]

End point description:

Vital signs included systolic blood pressure (BP), diastolic BP, heart rate, height, weight, respiratory rate, and body temperature. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Primary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 + 7 days after the last dose of study drug, approximately 19 weeks

Notes:

[4] - 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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: patients	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients with Clinically Significant Laboratory Abnormalities

End point title	Number of Patients with Clinically Significant Laboratory Abnormalities[5]

End point description:

Blood and urine samples were collected to determine the clinical chemistry, hematology, and urinalysis laboratory abnormalities. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Primary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 + 7 days after the last dose of study drug, approximately 19 weeks

Notes:

[5] - 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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: patients	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients with Clinically Significant 12-Lead Electrocardiogram (ECG) Abnormalities

End point title	Number of Patients with Clinically Significant 12-Lead Electrocardiogram (ECG) Abnormalities[6]

End point description:

Standard 12-lead ECGs were performed after the patient rested for 5 to 10 minutes. The ECG parameters included heart rate, PR interval, RR interval, QT interval, QTcF, and QRS interval from the triplicate 12-lead ECG. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Primary

End point timeframe:

From the first dose of study drug (Day 1) up to 30 + 7 days after the last dose of study drug, approximately 19 weeks

Notes:

[6] - 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: Only descriptive statistical analysis was performed for the primary endpoint.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: patients	1	0		

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 best overall response (BOR) of complete response (CR) or partial response (PR) as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The BOR was defined as the best response recorded from the start of study treatment until documented RECIST version 1.1 progression, death, or withdrawal of consent. 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 Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), Day 1 of

Cycle 3 and until confirmed objective disease progression. Up to approximately 19 weeks.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: percentage of patients				
number (confidence interval 95%)	0 (0.0 to 30.8)	0 (0.0 to 70.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

The DCR was defined as the percentage of patients with a BOR of CR, PR, or stable disease as determined by the investigator using RECIST version 1.1. Stable disease was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), Day 1 of Cycle 3 and until confirmed objective disease progression. Up to approximately 19 weeks.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: percentage of patients				
number (confidence interval 95%)	20.0 (2.5 to 55.6)	0 (0.0 to 70.8)		

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 treatment until the date of the first occurrence of PR or CR for responders only. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), Day 1 of Cycle 3 and until confirmed objective disease progression. Up to approximately 19 weeks.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[7] - No responders in this study.

[8] - No responders in this study.

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 occurrence of PR or CR whichever came first, until disease progression or death. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), Day 1 of Cycle 3 and until confirmed objective disease progression. Up to approximately 19 weeks.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[9] - No responders in this study.

[10] - No responders in this study.

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 treatment until the first radiographic documentation of objective progression as assessed by the investigator using RECIST version 1.1 or death from any cause. The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine. Here, 99999= The upper limit of 95% confidence interval could not be

estimated either due to insufficient number of PFS events or not sufficient follow-up time at the time of the analysis.

End point type	Secondary

End point timeframe:

RECIST assessments performed at baseline (within 28 days before start of study treatment), Day 1 of Cycle 3 and until confirmed objective disease progression. Up to approximately 19 weeks.

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	3		
Units: months				
median (confidence interval 95%)	1.8 (0.7 to 99999)	1.5 (1.1 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Performed Taste and Palatability Survey of Surufatinib

End point title	Number of Patients Who Performed Taste and Palatability Survey of Surufatinib

End point description:

The taste and palatability survey was assessed in patients who had taken surufatinib oral suspension. For pediatric patients, their parents completed the taste and palatability survey. Data for the evaluation of taste of surufatinib oral suspension was summarized on a scale of 1 (very bad) through 5 (very nice). The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

End point type	Secondary

End point timeframe:

Days 1 and 8 of Cycle 1

End point values	Dose Level 1	Dose Level 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	0[11]		
Units: patients				
number (not applicable)				
Cycle 1 Day 1: Very Nice	0			
Cycle 1 Day 1: Nice	1			
Cycle 1 Day 1: Not Nice, not Bad	0			
Cycle 1 Day 1: Bad	1			
Cycle 1 Day 1: Very Bad	0			
Cycle 1 Day 8: Very Nice	0			
Cycle 1 Day 8: Nice	1			
Cycle 1 Day 8: Not Nice, not Bad	0			
Cycle 1 Day 8: Bad	1			

Cycle 1 Day 8: Very Bad	0			

Notes:

[11] - No patients performed the survey.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs (TEAEs) were collected from the first dose of study drug (Day 1) up to 30 + 7 days after the last dose of study drug, approximately 19 weeks

Adverse event reporting additional description:

The Safety analysis set included all patients who received at least 1 dose of surufatinib or gemcitabine.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Dose Level 1

Reporting group description:

Participants received surufatinib 120 mg/m^2 oral capsule QD as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose IV infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until PD, unacceptable toxicity, or death; whichever came first.

Reporting group title	Dose Level 2

Reporting group description:

Participants received surufatinib 160 mg/m^2 oral capsule QD as a single agent for 14 days followed by surufatinib daily in combination with gemcitabine 1000 mg/m^2/dose IV infusion on Days 15 and 22 of a 35-day Cycle 1 and on Days 1 and 8 of 21-day subsequent cycles until PD, unacceptable toxicity, or death; whichever came first.

Serious adverse events	Dose Level 1	Dose Level 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 10 (70.00%)	1 / 3 (33.33%)	
number of deaths (all causes)	6	2	
number of deaths resulting from adverse events	2	0	
Nervous system disorders			
Spinal cord compression			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (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			
Pyrexia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			

subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Respiratory tract infection viral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (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	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Dose Level 1	Dose Level 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	3 / 3 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 10 (20.00%)	2 / 3 (66.67%)	
occurrences (all)	3	3	
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 10 (50.00%)	2 / 3 (66.67%)	
occurrences (all)	6	2	
Fatigue			
subjects affected / exposed	3 / 10 (30.00%)	2 / 3 (66.67%)	
occurrences (all)	4	2	
Non-cardiac chest pain			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Asthenia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Chills			

subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Gait disturbance			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 10 (30.00%)	2 / 3 (66.67%)	
occurrences (all)	5	2	
Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	2 / 3 (66.67%)	
occurrences (all)	2	2	
Atelectasis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			

subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Acute respiratory failure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 10 (30.00%)	3 / 3 (100.00%)	
occurrences (all)	3	5	
Neutrophil count decreased			
subjects affected / exposed	5 / 10 (50.00%)	1 / 3 (33.33%)	
occurrences (all)	9	1	
Platelet count decreased			
subjects affected / exposed	4 / 10 (40.00%)	1 / 3 (33.33%)	
occurrences (all)	11	1	
White blood cell count decreased			
subjects affected / exposed	3 / 10 (30.00%)	2 / 3 (66.67%)	
occurrences (all)	6	3	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 10 (20.00%)	2 / 3 (66.67%)	
occurrences (all)	4	2	
Alanine aminotransferase increased			

subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
International normalised ratio increased			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Lymphocyte count decreased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	7	4	
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Blood bicarbonate decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Prothrombin time prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Skin abrasion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Wound dehiscence			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Cardiac disorders			

Sinus tachycardia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Pericardial effusion			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	
occurrences (all)	3	1	
Dizziness			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 10 (60.00%)	2 / 3 (66.67%)	
occurrences (all)	16	5	
Eosinophilia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 3 (66.67%)	
occurrences (all)	0	4	
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Thrombocytosis			

subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 10 (50.00%)	2 / 3 (66.67%)	
occurrences (all)	10	3	
Vomiting			
subjects affected / exposed	5 / 10 (50.00%)	2 / 3 (66.67%)	
occurrences (all)	6	3	
Diarrhoea			
subjects affected / exposed	4 / 10 (40.00%)	1 / 3 (33.33%)	
occurrences (all)	8	1	
Constipation			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	
occurrences (all)	5	1	
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Oral pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Paraesthesia oral			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			

Acne			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin ulcer			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	4 / 10 (40.00%)	1 / 3 (33.33%)	
occurrences (all)	6	3	
Haematuria			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	2	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 10 (20.00%)	2 / 3 (66.67%)	
occurrences (all)	2	3	
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			

subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Pain in jaw			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Paronychia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Skin infection			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Bacteraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 10 (30.00%)	2 / 3 (66.67%)	
occurrences (all)	5	3	
Hypocalcaemia			
subjects affected / exposed	3 / 10 (30.00%)	1 / 3 (33.33%)	
occurrences (all)	7	1	
Hyperglycaemia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 3 (33.33%)	
occurrences (all)	2	2	
Hyperphosphataemia			

subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Hypokalaemia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 3 (0.00%)	
occurrences (all)	11	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Hypomagnesaemia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Hypermagnesaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Hypophosphataemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 October 2021	• Updated patient age limits. • Updated required number of patients for the Part 1 Pharmacokinetic (PK) expansion cohort. • Changed study duration to an estimated 36 months. • Updates to the schedule of PK sample collection. • Updates to the Schedule of Assessments table. • Revised inclusion criteria for reproductive potential. • Revised requirements for contraception. • Specified risks for gemcitabine. • Added a biomarker for evaluation.
03 March 2022	Administrative updates to update Sponsor's name.
24 January 2023	• Added language to indicate that enrollment was halted as of 16 December 2022. Following approval of Amendment 3, patients who were still enrolled were deriving clinical benefit from treatment were allowed to continue to participate in the study. • Revised number of patients in study from "Up to 116 patients" to "Up to 36 patients." • Updates to the efficacy endpoints.

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.

With the withdrawal of the Marketing Authorisation Application for surufatinib, the PIP was discontinued. As such, due to the small number of patients treated in this study, efficacy assessment was limited in this paediatric population.

Notes: