Clinical trial results:
Pivotal Study of Derazantinib in Patients With Inoperable or Advanced Intrahepatic Cholangiocarcinoma and FGFR2 Gene Fusions or FGFR2 Gene Mutations or Amplifications

Summary

EudraCT number	2016-004448-12
Trial protocol	IT GB DE IE ES
Global end of trial date	25 October 2022

Results information

Result version number	v1 (current)
This version publication date	10 November 2023
First version publication date	10 November 2023

Trial information

Trial identification

Sponsor protocol code	DZB-CS-301

Additional study identifiers

ISRCTN number	ISRCTN12345678
ClinicalTrials.gov id (NCT number)	NCT12345678
WHO universal trial number (UTN)	U1234-1234-1234

Notes:

Sponsors

Sponsor organisation name	Basilea Pharmaceutica International Ltd, Allschwil
Sponsor organisation address	Hegenheimermattweg 167b, Allschwil, Switzerland, 4123
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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	09 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 October 2022
Global end of trial reached?	Yes
Global end of trial date	25 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective
Substudy 1: To evaluate the anti-cancer activity by Objective Response Rate (ORR) by blinded independent central review as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in patients with inoperable or advanced iCCA whose tumors harbor FGFR2 fusions (by FISH performed by a central laboratory) and who received at least one prior regimen of systemic therapy.

Substudy 2: To evaluate the anti-tumor activity of derazantinib by progression-free survival at 3 months (PFS3) based on survival status or blinded independent central review (RECIST 1.1) in patients with inoperable or advanced iCCA whose tumors harbor FGFR2 mutations or amplifications, and who received at least one prior regimen of systemic therapy.

Protection of trial subjects:

The study was conducted according to the ethical principles that have their origins in the World Medical Association's Declaration of Helsinki, the International Council for Harmonisation (ICH) E6 Good Clinical Practice, and all applicable national and local laws and regulations for the conduct of clinical research and the protection of personal data. If conflicts between local laws and regulations arose, the more stringent requirements were adopted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 September 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	United States: 70
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 50
Worldwide total number of subjects	147
EEA total number of subjects	65

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)	102
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 729 patients underwent molecular screening, and 148 were enrolled. One patient was subsequently not confirmed to have fibroblast growth factor receptor 2 (FGFR2) fusion, and was excluded from the Safety/ITT population, meaning that for all Safety/ITT population analyses 147 patients were included (Substudy 1 = 103, Substudy = 44).

Period 1

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

Arms

Arm title	Derazantinib

Arm description:

Derazantinib was administered orally at 300 mg once daily

Arm type	Experimental
Investigational medicinal product name	Derazantinib
Investigational medicinal product code	BAL101553
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib, an investigational drug was supplied as 100 mg powder-filled capsules for oral administration in this open-label study. All patients received derazantinib at 300 mg once daily. Derazantinib capsules were administered 1 hour before, or at least 2 hours after, a meal.

Number of subjects in period 1	Derazantinib
Started	147
Completed	0
Not completed	147
Clinical progression	23
Adverse event, serious fatal	5
Physician decision	5
Consent withdrawn by subject	4
Radiographic disease progression	91
Adverse event, non-fatal	8
Other reasons	10
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	Derazantinib
Reporting group description:	
Derazantinib was administered orally at 300 mg once daily	

Reporting group values	Derazantinib	Total	
Number of subjects	147	147	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	58.0		
standard deviation	± 12.28	-	
Gender categorical Units: Subjects			
Female	92	92	
Male	55	55	
Race Units: Subjects			
Asian	7	7	
Black or African American	8	8	
White	123	123	
More than one race	5	5	
Unknown or Not Reported	4	4	

Subject analysis sets	
Subject analysis set title	Substudy 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
Substudy 1 (safety and intent-to-treat (ITT) population) comprised of patients with inoperable or advanced iCCA with FGFR2 fusions and who had received any amount of study drug Derazantinib was administered orally at 300 mg once daily	
Subject analysis set title	Substudy 2
Subject analysis set type	Safety analysis

Subject analysis set description:

Substudy 2 (safety and intent-to-treat (ITT) population) comprised of patients with with inoperable or advanced iCCA with FGFR2 mutations or amplifications and who had received any amount of study drug

Derazantinib was administered orally at 300 mg once daily

Subject analysis set title	mITT Substudy 2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT Population: included all patients in the Safety/ITT population, who had at least one post-baseline disease assessment (at least one post-baseline imaging assessment in accordance with RECIST 1.1, or documented clinical progression [every effort was made to objectively assess radiographic progression]), or reported death during the treatment period.

Reporting group values	Substudy 1	Substudy 2	mITT Substudy 2
Number of subjects	103	44	43
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	56.5	61.3	
standard deviation	± 12.28	± 11.75	±
Gender categorical			
Units: Subjects			
Female	67	25	
Male	36	19	
Race			
Units: Subjects			
Asian	3	4	
Black or African American	8	0	
White	86	37	
More than one race	4	1	
Unknown or Not Reported	2	2	

End points

End points reporting groups

Reporting group title	Derazantinib

Reporting group description:

Derazantinib was administered orally at 300 mg once daily

Subject analysis set title	Substudy 1
Subject analysis set type	Safety analysis

Subject analysis set description:

Substudy 1 (safety and intent-to-treat (ITT) population) comprised of patients with inoperable or advanced iCCA with FGFR2 fusions and who had received any amount of study drug

Derazantinib was administered orally at 300 mg once daily

Subject analysis set title	Substudy 2
Subject analysis set type	Safety analysis

Subject analysis set description:

Substudy 2 (safety and intent-to-treat (ITT) population) comprised of patients with with inoperable or advanced iCCA with FGFR2 mutations or amplifications and who had received any amount of study drug

Derazantinib was administered orally at 300 mg once daily

Subject analysis set title	mITT Substudy 2
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

mITT Population: included all patients in the Safety/ITT population, who had at least one post-baseline disease assessment (at least one post-baseline imaging assessment in accordance with RECIST 1.1, or documented clinical progression [every effort was made to objectively assess radiographic progression]), or reported death during the treatment period.

Primary: Substudy 1: Objective Response Rate (ORR)

End point title	Substudy 1: Objective Response Rate (ORR)[1]

End point description:

ORR was defined as the proportion of patients who achieved a confirmed clinical response (CR) or partial response (PR) by blinded independent central review using the internationally recognized criteria for the radiological assessment in tumor response of solid tumors (RECIST) Version 1.1

End point type	Primary

End point timeframe:

From first dose and up to 54 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: There is no comparator group for a statistical analysis. The statistical analysis is of descriptive nature.

End point values	Substudy 1			
Subject group type	Subject analysis set			
Number of subjects analysed	103			
Units: Proportion of patients				
number (confidence interval 95%)	22.3 (14.7 to 31.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Substudy 2: Progression Free Survival at 3 Months (PFS 3)

End point title	Substudy 2: Progression Free Survival at 3 Months (PFS 3)[2]

End point description:

PFS was calculated from the first date of receiving study drug until radiographic disease progression by blinded independent central review or death.

End point type	Primary

End point timeframe:

From first dose and up to 54 months

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: There is no comparator group for a statistical analysis. The statistical analysis is of descriptive nature.

End point values	mITT Substudy 2			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Percentage of participants				
number (confidence interval 95%)	62.8 (46.7 to 77.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was calculated from the first date of receiving study drug until death

End point type	Secondary

End point timeframe:

From first dose and up to 54 months

End point values	Substudy 1	Substudy 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	44		
Units: Months				
median (confidence interval 95%)	17.2 (12.5 to 22.4)	11.9 (8.4 to 15.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Substudy 2: Objective Response Rate

End point title	Substudy 2: Objective Response Rate

End point description:

ORR was defined as the proportion of patients who achieved a confirmed clinical response (CR) or partial response (PR) by blinded independent central review using the internationally recognized criteria for the radiological assessment in tumor response of solid tumors (RECIST) Version 1.1.

End point type	Secondary

End point timeframe:

From first dose and up to 54 months

End point values	mITT Substudy 2			
Subject group type	Subject analysis set			
Number of subjects analysed	43			
Units: Percentage of participants				
number (confidence interval 95%)	9.3 (2.6 to 22.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Grade 3-5 Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Patients With Grade 3-5 Treatment-emergent Adverse Events (TEAEs)

End point description:

Number of patients experiencing TEAE of Grade 3 to 5 according to Common Terminology Criteria for Adverse Events (CTCAE)

End point type	Secondary

End point timeframe:

TEAEs were defined as all events occurring after drug treatment began and up to 30 days after last study drug
administration

End point values	Substudy 1	Substudy 2		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	103	44		
Units: Number of patients				
Patients with unrelated TEAEs of Grade 3-5	31	16		
Patients with related TEAEs of Grade 3-5	35	10		
Patients without TEAEs of Grade 3-5	37	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first administration of study medication up to 30 days after the last administration.	
Adverse event reporting additional description:	
Treatment-emergent adverse events and serious adverse events	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Substudy 1
Reporting group description:	
Substudy 1	
Reporting group title	Substudy 2
Reporting group description:	
Substudy 2	

Serious adverse events	Substudy 1	Substudy 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 103 (35.92%)	16 / 44 (36.36%)	
number of deaths (all causes)	74	25	
number of deaths resulting from adverse events	11	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Liver transplant			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	9 / 103 (8.74%)	3 / 44 (6.82%)	
occurrences causally related to treatment / all	0 / 9	0 / 3	
deaths causally related to treatment / all	0 / 9	0 / 3	
General physical health deterioration			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 103 (0.97%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 103 (0.97%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oropharyngeal pain			

subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 103 (1.94%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	2 / 103 (1.94%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Traumatic intracranial haematoma			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrioventricular block second degree			

subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Tremor			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Ascites			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticular perforation			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	6 / 103 (5.83%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	2 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			

subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 103 (0.97%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 103 (0.97%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bacteraemia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 103 (0.97%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 103 (0.00%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 103 (0.97%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			

subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 103 (0.97%)	0 / 44 (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			
Hyponatraemia			
subjects affected / exposed	2 / 103 (1.94%)	1 / 44 (2.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Substudy 1	Substudy 2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	103 / 103 (100.00%)	43 / 44 (97.73%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 103 (23.30%)	5 / 44 (11.36%)	
occurrences (all)	30	7	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	7 / 103 (6.80%)	2 / 44 (4.55%)	
occurrences (all)	9	2	
Oedema peripheral			
subjects affected / exposed	5 / 103 (4.85%)	4 / 44 (9.09%)	
occurrences (all)	5	5	
Mucosal inflammation			
subjects affected / exposed	3 / 103 (2.91%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
Fatigue			

subjects affected / exposed	34 / 103 (33.01%)	13 / 44 (29.55%)	
occurrences (all)	37	16	
Asthenia			
subjects affected / exposed	25 / 103 (24.27%)	6 / 44 (13.64%)	
occurrences (all)	27	8	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	9 / 103 (8.74%)	3 / 44 (6.82%)	
occurrences (all)	9	3	
Dyspnoea			
subjects affected / exposed	10 / 103 (9.71%)	2 / 44 (4.55%)	
occurrences (all)	10	3	
Cough			
subjects affected / exposed	14 / 103 (13.59%)	7 / 44 (15.91%)	
occurrences (all)	15	7	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	15 / 103 (14.56%)	0 / 44 (0.00%)	
occurrences (all)	15	0	
Depression			
subjects affected / exposed	7 / 103 (6.80%)	1 / 44 (2.27%)	
occurrences (all)	7	1	
Anxiety			
subjects affected / exposed	8 / 103 (7.77%)	2 / 44 (4.55%)	
occurrences (all)	8	2	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	46 / 103 (44.66%)	13 / 44 (29.55%)	
occurrences (all)	52	15	
Blood alkaline phosphatase increased			
subjects affected / exposed	17 / 103 (16.50%)	9 / 44 (20.45%)	
occurrences (all)	18	11	
Alanine aminotransferase increased			
subjects affected / exposed	36 / 103 (34.95%)	13 / 44 (29.55%)	
occurrences (all)	43	15	
Blood phosphorus increased			

subjects affected / exposed	13 / 103 (12.62%)	2 / 44 (4.55%)	
occurrences (all)	20	2	
Blood creatinine increased			
subjects affected / exposed	17 / 103 (16.50%)	7 / 44 (15.91%)	
occurrences (all)	18	8	
White blood cell count decreased			
subjects affected / exposed	6 / 103 (5.83%)	3 / 44 (6.82%)	
occurrences (all)	11	3	
Neutrophil count decreased			
subjects affected / exposed	4 / 103 (3.88%)	3 / 44 (6.82%)	
occurrences (all)	6	3	
Weight decreased			
subjects affected / exposed	17 / 103 (16.50%)	6 / 44 (13.64%)	
occurrences (all)	17	6	
Platelet count decreased			
subjects affected / exposed	10 / 103 (9.71%)	5 / 44 (11.36%)	
occurrences (all)	20	5	
Nervous system disorders			
Dizziness			
subjects affected / exposed	13 / 103 (12.62%)	3 / 44 (6.82%)	
occurrences (all)	13	3	
Dysgeusia			
subjects affected / exposed	20 / 103 (19.42%)	11 / 44 (25.00%)	
occurrences (all)	20	11	
Headache			
subjects affected / exposed	12 / 103 (11.65%)	5 / 44 (11.36%)	
occurrences (all)	14	6	
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 103 (0.97%)	3 / 44 (6.82%)	
occurrences (all)	1	3	
Tremor			
subjects affected / exposed	8 / 103 (7.77%)	1 / 44 (2.27%)	
occurrences (all)	9	1	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	16 / 103 (15.53%)	6 / 44 (13.64%)	
occurrences (all)	18	6	
Thrombocytopenia			
subjects affected / exposed	7 / 103 (6.80%)	1 / 44 (2.27%)	
occurrences (all)	8	1	
Eye disorders			
Cornea verticillata			
subjects affected / exposed	7 / 103 (6.80%)	1 / 44 (2.27%)	
occurrences (all)	7	1	
Dry eye			
subjects affected / exposed	20 / 103 (19.42%)	7 / 44 (15.91%)	
occurrences (all)	20	7	
Keratitis			
subjects affected / exposed	2 / 103 (1.94%)	3 / 44 (6.82%)	
occurrences (all)	2	3	
Vision blurred			
subjects affected / exposed	26 / 103 (25.24%)	6 / 44 (13.64%)	
occurrences (all)	26	8	
Xerophthalmia			
subjects affected / exposed	9 / 103 (8.74%)	5 / 44 (11.36%)	
occurrences (all)	11	6	
Visual impairment			
subjects affected / exposed	5 / 103 (4.85%)	3 / 44 (6.82%)	
occurrences (all)	5	4	
Visual acuity reduced			
subjects affected / exposed	7 / 103 (6.80%)	0 / 44 (0.00%)	
occurrences (all)	7	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	26 / 103 (25.24%)	6 / 44 (13.64%)	
occurrences (all)	30	6	
Abdominal distension			
subjects affected / exposed	3 / 103 (2.91%)	3 / 44 (6.82%)	
occurrences (all)	3	3	
Abdominal pain upper			

subjects affected / exposed	10 / 103 (9.71%)	1 / 44 (2.27%)	
occurrences (all)	12	1	
Vomiting			
subjects affected / exposed	30 / 103 (29.13%)	15 / 44 (34.09%)	
occurrences (all)	43	23	
Nausea			
subjects affected / exposed	41 / 103 (39.81%)	18 / 44 (40.91%)	
occurrences (all)	51	23	
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 103 (5.83%)	1 / 44 (2.27%)	
occurrences (all)	6	2	
Dyspepsia			
subjects affected / exposed	10 / 103 (9.71%)	2 / 44 (4.55%)	
occurrences (all)	10	2	
Dry mouth			
subjects affected / exposed	30 / 103 (29.13%)	17 / 44 (38.64%)	
occurrences (all)	32	17	
Diarrhoea			
subjects affected / exposed	34 / 103 (33.01%)	14 / 44 (31.82%)	
occurrences (all)	52	21	
Constipation			
subjects affected / exposed	28 / 103 (27.18%)	8 / 44 (18.18%)	
occurrences (all)	31	10	
Skin and subcutaneous tissue disorders			
Nail discolouration			
subjects affected / exposed	2 / 103 (1.94%)	3 / 44 (6.82%)	
occurrences (all)	2	3	
Dry skin			
subjects affected / exposed	14 / 103 (13.59%)	3 / 44 (6.82%)	
occurrences (all)	14	3	
Alopecia			
subjects affected / exposed	16 / 103 (15.53%)	6 / 44 (13.64%)	
occurrences (all)	17	6	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	13 / 103 (12.62%)	1 / 44 (2.27%)	
occurrences (all)	13	1	
Back pain			
subjects affected / exposed	15 / 103 (14.56%)	0 / 44 (0.00%)	
occurrences (all)	15	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	9 / 103 (8.74%)	2 / 44 (4.55%)	
occurrences (all)	9	3	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	20 / 103 (19.42%)	9 / 44 (20.45%)	
occurrences (all)	23	9	
Dehydration			
subjects affected / exposed	6 / 103 (5.83%)	2 / 44 (4.55%)	
occurrences (all)	6	2	
Hypercalcaemia			
subjects affected / exposed	11 / 103 (10.68%)	3 / 44 (6.82%)	
occurrences (all)	11	3	
Hyperphosphataemia			
subjects affected / exposed	30 / 103 (29.13%)	12 / 44 (27.27%)	
occurrences (all)	36	14	
Hypoalbuminaemia			
subjects affected / exposed	7 / 103 (6.80%)	2 / 44 (4.55%)	
occurrences (all)	9	2	
Hyponatraemia			
subjects affected / exposed	8 / 103 (7.77%)	4 / 44 (9.09%)	
occurrences (all)	8	4	
Vitamin D deficiency			
subjects affected / exposed	6 / 103 (5.83%)	2 / 44 (4.55%)	
occurrences (all)	6	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 April 2017	• Change the in vitro companion diagnostic device (IVD) designated for use in the trial • As an addition to Section 3.1, blood samples for tumor markers were to be collected for all enrolled subjects. Blood samples for biomarkers and ctDNA were to be collected only if the study passed the interim analysis and collected from newly enrolled subjects.
13 April 2017	• Clarified that medication could be administered with or without food • Clarifications added concerning exploratory objective and efficacy endpoints • 'Creatinine clearance of ≥ 60 mL/min as estimated by the Cockcroft-Gault equation' was added to the inclusion criteria • It was clarified in Section 6.7 Tumor Biopsy, that 'archived tissue specimens may be submitted if they meet the requirements outlined in the Laboratory Manual.' • Section 10.6.3 Exploratory Efficacy Analyses was augmented to include that 'Other analyses such as correlation between tumor and biomarkers, toxicity, responses, and PK parameters to be conducted and to be further described in the Statistical Analysis Plan.'
10 October 2017	• Made minor change to title page to clarify the designation of the study as phase 2 rather than phase 3. This change was also reflected in the synopsis and elsewhere if noted. • Added the name of the medical monitor to title page.

25 September 2018	• The change in sponsorship from ArQule Inc. to Basilea Pharmaceutica International Ltd. was implemented in the protocol. • The exploratory evaluation of ORR using modified RECIST criteria was removed from the protocol. • The exploratory objectives were amended so that time to progression by blinded independent central review for derazantinib was to be evaluated overall, and not only by line of prior systemic therapy. The associated exploratory endpoints were updated for consistency. • Inclusion criterion 4 was changed to clarify the approach to the assessment of FGFR2 gene fusion status for the purposes of enrollment. Similar clarification was added to other related sections of the protocol. • Additional ECG assessments were scheduled to coincide with each collection of a plasma sample for pharmacokinetic assessment. • The protocol and Informed Consent Form were changed to specify that metabolites of derazantinib could be assessed from the same samples already planned to determine the population PK parameters of derazantinib. • Change of the safety vendor. • Text restricting the 30-day safety follow-up to adverse events thought to be related to study drug was deleted. • The definition of a related adverse event was clarified to include any adverse event considered definitely, probably, or possibly related to derazantinib, or when the relationship is unknown. • The reference to treatment groups was removed from Section 10.3 (Safety Analyses), along with consistency corrections in the same section. • A change was made to permit an earlier interim analysis if 5 or more objective responses were observed and confirmed based on blinded independent central review before the the previously-required enrollment of 40 evaluable patients

19 February 2019	• Study expanded by adding a separate group of patients with FGFR2 gene mutations or amplifications to assess the potential expanded utility of derazantinib in the treatment of iCCA. • The original primary objective of the study was adjusted to allow both the original patients (now termed Substudy 1 and Substudy 2) to be included in the primary objectives. The primary objective of Substudy 2 was to evaluate the anti-tumor activity of derazantinib by progression-free survival at 3 months (PFS3). • Addressed requests by Health Authorities among others considering Clinical Trial Applications in additional countries, including: Revision of sections related to pregnancy and contraception; revision of sections related to QT/QTc; revision of sections related to UV-light protection. • Implemented central ECG assessments. • Defined subgroups of patients who underwent a more intensive biomarker and/or PK assessment schedule. • Clarifications added concerning screening procedures for genomic aberrations. • The secondary objectives of the study were amended to include for Substudy 2 an objective to evaluate the anti-cancer activity by ORR by central radiology. • Exploratory endpoints were added. • For patient-reported outcomes, an additional outcome for HRQOL (the EuroQoL-5D visual analog scale) was included. • Various inclusion and exclusion criteria were updated • A complete eye examination was added to the list of assessments to be conducted at the 30-day Safety Follow-up Visit. • Relevant examinations and laboratory tests were updated • Provision for informed consent to participate in the study to be provided by the patient's legal representative was removed.
22 July 2019	• Section 3.4 was amended to clarify that for patients who demonstrate continued benefit from derazantinib at the time of study closure, the Sponsor aims to provide continued access to derazantinib. • Clarified that patients considered eligible for enrollment in Substudy 2 should have exhausted all satisfactory treatment alternatives. • Exclusion criterion 9 was amended to require patients enrolled in the study to have serum potassium levels within normal ranges. • Section 7.3.3 was clarified that in the event of a prolonged QTc interval ≥ 501 ms being observed on at least two separate ECGs (CTCAE v4.03 Grade 3 event), derazantinib was to be withheld until the QTc has returned to ≤ 470 msec, and a decision made whether to continue treatment with derazantinib. • Clarified the position for patients who were enrolled and dosed on the basis of a positive local test result for FGFR2 gene fusion (Substudy 1). • For the management of patients whose FGFR2 gene fusion status was not centrally confirmed after treatment has commenced, the a case by case assessment was required for these patients. • Inclusion criterion 9 was amended to ensure that 'highly effective' contraceptive measures were required during the study; 'acceptable' birth control methods were not sufficient. • Clarifications to tumor assessment methods were added. • Clarification in Appendix 8 (List of FGFR2 mutations eligible for enrollment in Substudy 2) that newly detected mutations could be added to the list

06 September 2019	• CYP2C8 ligands were added to the list of CYP enzymes in Appendix 4, substrates of which should be avoided or used with caution. • A requirement was added to Section 6.8 for patients who discontinue study drug treatment to have a tumor assessment as soon as possible after discontinuation. • It was clarified that the Substudy 2 sample size refers to mITT-evaluable patients. • Section 10.7 was amended to clarify that in Substudy 2, a decision to proceed with Stage 2 or stop for futility was to be made as soon as the number of events allows it, and that enrollment in Stage 2 was to be suspended if the required number of patients was not reached at the time of full enrollment to Stage 1. • Time windows were introduced for PK sample collection and the collection of the 10 and 12 hours samples was made optional. • The list of FGFR2 mutations eligible for enrollment in Substudy 2 was updated in Appendix 8.
17 November 2020	• Details were added throughout the protocol update and clarify details of alternative NGS testing options for prospective patient enrollment in Substudy 2. • The FGFR2 genetic aberration status required for eligibility for Substudy 2 was clarified, along with the testing requirements. • The definition of adequate renal function for eligibility for enrollment into the study, was updated to a creatinine clearance of ≥ 30 mL/min as estimated by the Cockcroft-Gault equation. • Details regarding prohibited prior anti-cancer treatments were updated. • Further clarification was made regarding previous treatments with an FGFR inhibitor, which exclude the patient from eligibility for the study. • Further details were added regarding ophthalmological exclusion criteria. • Patients with any severe infections were added to exclusions from study . • References to a biomarker study were changed to pharmacodynamic assessments, and the processes for collecting archival tumor and blood and urine samples, and for conducting pharmacodynamic analyses, were clarified accordingly. • Administration of derazantinib with a light meal was permitted in the event of nausea or vomiting which is assessed as moderate (CTCAE Grade ≥ 2). • Advice relating to dose delays/reductions in the event of a CTCAE Grade 4 adverse event was revised. • The CSP was updated to include a new requirement to perform complete ophthalmological examination. • Transaminase elevations (AST and ALT increased) were removed from the list of potential risks, and upgraded to an identified risk. Phototoxicity was removed from the list of potential risks. The list of important potential risks was updated to include hyponatremia, and redefined ‘creatinine increase’ as ‘blood creatinine increased / renal disorders’. • Removed the list of FGFR2 genetic aberrations (GAs) eligible for enrollment in Substudy 2 from Appendix 8, in favor of a description of the categories of applicable GAs

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.

The following secondary endpoints could not be shown due to the restrictions of the EudraCT system; duration of response and progression free survival. The figures are on CT.gov: https://clinicaltrials.gov/study/NCT03230318

Notes: