Clinical trial results:
A Phase 1b/2 study of derazantinib as monotherapy and combination therapy with paclitaxel, ramucirumab or atezolizumab in patients with HER2-negative gastric adenocarcinoma harboring FGFR genetic aberrations (FIDES-03)

Summary

EudraCT number	2019-004505-27
Trial protocol	GB DE FR BE IT
Global end of trial date	21 November 2022

Results information

Result version number	v1 (current)
This version publication date	07 December 2023
First version publication date	07 December 2023

Trial information

Trial identification

Sponsor protocol code	DZB-CS-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04604132
WHO universal trial number (UTN)	-

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	13 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 November 2022
Global end of trial reached?	Yes
Global end of trial date	21 November 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Substudy 1
The primary objective for Cohorts 1.1 and 1.2 was to evaluate the overall response rate (ORR) of patients with HER2neg FGFR2fus/amp (Cohort 1.1) and FGFR1-3mt (Cohort 1.2) GAC treated with derazantinib monotherapy (300 mg QD). For Cohort 1.3, the primary objective was to evaluate the progression-free survival at 4 months (PFS4) of patients with HER2neg FGFRfus/amp/mt GAC treated with derazantinib monotherapy (200 mg BID).
Substudy 2
The primary objective of Substudy 2 was to determine the recommended Phase 2 dose (RP2D) of derazantinib-paclitaxel-ramucirumab in combination in patients with HER2neg FGFRfus/amp/mt GAC.

The study originally planned to include three substudies but was prematurely terminated for administrative reasons before the third substudy (including combination therapy with derazantinib plus atezolizumab) was initiated.

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	06 October 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1
Country: Number of subjects enrolled	Australia: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Korea, Republic of: 9

Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Turkey: 4
Worldwide total number of subjects	47
EEA total number of subjects	17

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)	32
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

From 6 October 2020 to 10 June 2022, 919 patients underwent molecular pre-screening. 66 then underwent clinical screening, and 47 were then assigned treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily

Arm description:

Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in the Substudy 1.

Arm type	Experimental
Investigational medicinal product name	Derazantinib in Substudy 1, Cohort 1.1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in Substudy 1.

All patients were treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the cohort, substudy, or the study was terminated by the Sponsor, whichever occurred first

Investigational medicinal product name	Derazantinib-paclitaxel-ramucirumab combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Derazantinib was administered orally at a dose of either 200, 300 mg once daily or 200 mg twice daily in combination with paclitaxel and ramucirumab in the Substudy 2.

Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab.

Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel.

All patients were treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the cohort, substudy, or the study was terminated by the Sponsor, whichever occurred first

Arm title	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily

Arm description:

Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in the Substudy 1.

Arm type	Experimental

Investigational medicinal product name	Derazantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in Substudy 1.

All patients were treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the cohort, substudy, or the study was terminated by the Sponsor, whichever occurred first

Arm title	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily

Arm description:

Derazantinib was administered orally at a dose of 200 mg twice daily as monotherapy in the Substudy 1.

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

Dosage and administration details:

Derazantinib was administered orally at a dose of 200 mg twice daily as monotherapy in the Substudy 1.

All patients were treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the cohort, substudy, or the study was terminated by the Sponsor, whichever occurred first

Arm title	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab

Arm description:

Derazantinib-paclitaxel-ramucirumab combination: Derazantinib was administered orally at a dose of 200 mg once daily in combination with paclitaxel and ramucirumab.
Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab.
Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel

Arm type	Experimental
Investigational medicinal product name	Derazantinib-paclitaxel-ramucirumab combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Derazantinib was administered orally at a dose of 200 mg once daily in combination with paclitaxel and ramucirumab in the Substudy 2.

Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab.

Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel.

All patients were treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the cohort, substudy, or the study was terminated by the Sponsor, whichever occurred first

Arm title	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab

Arm description:

Derazantinib-paclitaxel-ramucirumab combination: Derazantinib was administered orally at a dose of either 300 mg once daily or 200 mg twice daily in combination with paclitaxel and ramucirumab.

Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab.
Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel.

Arm type	Experimental
Investigational medicinal product name	Derazantinib-paclitaxel-ramucirumab combination
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Concentrate for solution for infusion
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Derazantinib was administered orally at a dose of either 300 mg once daily or 200 mg twice daily in combination with paclitaxel and ramucirumab in Substudy 2.

Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab.

Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel.

All patients were treated until disease progression, patient withdrawal, patient lost to follow up, or unacceptable toxicity, or until the Investigator's decision to remove the patient from treatment, or until the cohort, substudy, or the study was terminated by the Sponsor, whichever occurred first

Number of subjects in period 1	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily
Started	13	8	13
Completed	0	0	0
Not completed	13	8	13
Adverse event, serious fatal	3	1	2
Adverse event, non-fatal	2	-	-
Study terminated by sponsor	-	-	-
Progressive disease: Radiological progression	8	7	10
Progressive disease: Clinical progression	-	-	1

Number of subjects in period 1	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab
Started	6	7
Completed	0	1
Not completed	6	6
Adverse event, serious fatal	1	-
Adverse event, non-fatal	1	2
Study terminated by sponsor	-	1
Progressive disease: Radiological progression	4	3
Progressive disease: Clinical progression	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily
Reporting group description:	
Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in the Substudy 1.	
Reporting group title	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily
Reporting group description:	
Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in the Substudy 1.	
Reporting group title	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily
Reporting group description:	
Derazantinib was administered orally at a dose of 200 mg twice daily as monotherapy in the Substudy 1.	
Reporting group title	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab
Reporting group description:	
Derazantinib-paclitaxel-ramucirumab combination: Derazantinib was administered orally at a dose of 200 mg once daily in combination with paclitaxel and ramucirumab. Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab. Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel	
Reporting group title	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab
Reporting group description:	
Derazantinib-paclitaxel-ramucirumab combination: Derazantinib was administered orally at a dose of either 300 mg once daily or 200 mg twice daily in combination with paclitaxel and ramucirumab. Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab. Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel.	

Reporting group values	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily
Number of subjects	13	8	13
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	65.5	66.1	54.8
standard deviation	± 10.77	± 9.39	± 13.43

Gender categorical Units: Subjects			
Female	5	2	1
Male	8	6	12
Race Units: Subjects			
Asian	4	1	2
Black or African American	0	0	1
White	9	7	9
Missing	0	0	1

Reporting group values	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab	Total
Number of subjects	6	7	47
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	55.2	52.0	
standard deviation	± 10.53	± 11.34	-
Gender categorical Units: Subjects			
Female	1	5	14
Male	5	2	33
Race Units: Subjects			
Asian	0	2	9
Black or African American	0	0	1
White	6	5	36
Missing	0	0	1

End points

End points reporting groups

Reporting group title	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily

Reporting group description:

Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in the Substudy 1.

Reporting group title	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily

Reporting group description:

Derazantinib was administered orally at a dose of 300 mg once daily as monotherapy in the Substudy 1.

Reporting group title	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily

Reporting group description:

Derazantinib was administered orally at a dose of 200 mg twice daily as monotherapy in the Substudy 1.

Reporting group title	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab

Reporting group description:

Derazantinib-paclitaxel-ramucirumab combination: Derazantinib was administered orally at a dose of 200 mg once daily in combination with paclitaxel and ramucirumab.
Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab.
Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel

Reporting group title	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab

Reporting group description:

Derazantinib-paclitaxel-ramucirumab combination: Derazantinib was administered orally at a dose of either 300 mg once daily or 200 mg twice daily in combination with paclitaxel and ramucirumab.

Paclitaxel was administered intravenously at a dose of 80 mg/m² on days 1, 8, and 15 of a 28-day cycle in combination with ramucirumab.
Ramucirumab was administered intravenously at a dose of 8 mg/kg every 2 weeks in combination with paclitaxel.

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

Subject analysis set description:

The Maximum Tolerated Dose (MTD)-determining population comprised all patients enrolled in Substudy 2 who meet the minimum criteria during the first 28-day treatment cycle (Cycle 1):
received at least one dose of derazantinib-paclitaxel-ramucirumab in combination and has experienced a DLT
or
received ≥ 80% of the derazantinib-paclitaxel-ramucirumab dose, respectively, in Cycle 1 and, had been observed for ≥ 28 days following the first dose, and had been evaluated for safety.

Subject analysis set title	Substudy 1 Combined
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Derazantinib was administered orally at a dose of either 300 mg once daily or at a dose of 200 mg twice daily as monotherapy in Substudy 1.

Primary: Objective Response Rate (ORR) in Substudy 1 (in Cohorts 1.1 and 1.2)

End point title	Objective Response Rate (ORR) in Substudy 1 (in Cohorts 1.1 and 1.2)[1][2]

End point description:

ORR was defined by the proportion of patients with confirmed complete response (CR) or partial response (PR) by blinded independent central review (BICR) using the internationally recognized criteria for the radiological assessment in tumor response of solid tumors (RECIST 1.1).
The patients in Cohort 1.1 had FGFR2 fusions or amplification gastric adenocarcinoma (GAC) and FGFR1-3 mutations GAC in Cohort 1.2.

End point type	Primary

End point timeframe:

From first dose and up to 30 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: This study was not powered for formal statistical analysis.

[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: This study was not powered for formal statistical analysis.

End point values	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: Percentage of participants				
number (confidence interval 90%)	0.0 (0.0 to 20.6)	0.0 (0.0 to 31.2)		

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free Survival at 4 Months (PFS4) in Substudy 1 in Cohort 1.3

End point title	Progression-free Survival at 4 Months (PFS4) in Substudy 1 in Cohort 1.3[3][4]

End point description:

PFS4 was defined by the proportion of patients alive and free of disease progression by BICR per RECIST. 1.1. Patients in this Cohort had HER2negative FGFR fusions, amplfications or mutations GAC

End point type	Primary

End point timeframe:

From first dose and up to 4 months

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: This study was not powered for formal statistical analysis.

[4] - 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: This study was not powered for formal statistical analysis.

End point values	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage of participants				
number (confidence interval 90%)	7.7 (0.4 to 31.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Recommended Phase 2 Dose (RP2D) in Substudy 2 (Derazantinib-paclitaxel-ramucirumab in Combination)

End point title	Recommended Phase 2 Dose (RP2D) in Substudy 2 (Derazantinib-paclitaxel-ramucirumab in Combination)[5]

End point description:

RP2D was determined from safety and tolerability according to the aggregate of dose-limiting toxicity criteria and adverse event (AE) data, and considering further pharmacokinetic and efficacy data of the derazantinib-paclitaxel-ramucirumab combination in patients with FGFR fusions, amplifications or mutations GAC.

End point type	Primary

End point timeframe:

From first dose and up to 18 months

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: This study was not powered for formal statistical analysis.

End point values	Substudy 2 Combined			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: mg				
number (not applicable)	200			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Substudy 1 in Cohort 1.3

End point title	ORR in Substudy 1 in Cohort 1.3[6]

End point description:

ORR was defined by the proportion of patients with CR or PR by BICR according to RECIST Version 1.1

End point type	Secondary

End point timeframe:

From first dose and up to 9 months

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This study was not powered for formal statistical analysis.

End point values	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Percentage of participants				
number (confidence interval 90%)	0.0 (0.0 to 20.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) in Substudy 1: Cohort 1.1, 1.3 and 1.3 and Combined Cohorts

End point title	Disease Control Rate (DCR) in Substudy 1: Cohort 1.1, 1.3 and 1.3 and Combined Cohorts[7]

End point description:

Defined as the proportion of patients with confirmed CR, PR or stable disease (SD) by BICR per RECIST version 1.1.

End point type	Secondary

End point timeframe:

From first dose and up to 18 months

Notes:

[7] - 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: This study was not powered for formal statistical analysis.

End point values	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily	Substudy 1 Combined
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	13	8	13	34
Units: Percentage of participants				
number (confidence interval 90%)	30.8 (11.3 to 57.3)	25.0 (4.6 to 60.0)	15.4 (2.8 to 41.0)	23.5 (12.3 to 38.5)

Statistical analyses

No statistical analyses for this end point

Secondary: PFS in Substudy 1 in Cohort 1.3

End point title	PFS in Substudy 1 in Cohort 1.3[8]

End point description:

PFS was calculated from patient enrollment to progressive disease (PD) date by BICR per RECIST version 1.1

End point type	Secondary

End point timeframe:

From first dose and up to 9 months

Notes:

[8] - 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: This study was not powered for formal statistical analysis.

End point values	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Months				
number (confidence interval 90%)	1.7 (1.0 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in Substudy 1 in Cohort 1.3

End point title	Overall Survival (OS) in Substudy 1 in Cohort 1.3[9]

End point description:

OS was measured from patient enrollment to time of death.

End point type	Secondary

End point timeframe:

From first dose and up to 9 months

Notes:

[9] - 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: This study was not powered for formal statistical analysis.

End point values	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Months				
median (confidence interval 95%)	3.3 (2.2 to 3.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: ORR in Substudy 2

End point title	ORR in Substudy 2[10]

End point description:

ORR was defined by the proportion of patients with CR or PR by BICR per RECIST version 1.1.

End point type	Secondary

End point timeframe:

From first dose and up to 15 months

Notes:

[10] - 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: This study was not powered for formal statistical analysis.

End point values	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	7		
Units: Percentage of participants				
number (confidence interval 90%)	40.0 (7.6 to 81.1)	57.1 (22.5 to 87.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: DCR in Substudy 2

End point title	DCR in Substudy 2[11]

End point description:

Defined as the proportion of patients with confirmed CR, PR or SD by BICR per RECIST version 1.1.

End point type	Secondary

End point timeframe:

From first dose and up to 15 months

Notes:

[11] - 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: This study was not powered for formal statistical analysis.

End point values	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab	Substudy 2 Combined	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	5	7	12	
Units: Percentage of participants				
number (confidence interval 90%)	80.0 (34.3 to 99.0)	71.4 (34.1 to 94.7)	75.0 (47.3 to 92.8)	

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

End point type	Secondary

End point timeframe:

Treatment emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity on or after the first dose of study treatment and until safety follow-up visit (inclusive).

End point values	Substudy 1: Cohort 1.1 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.2 Derazantinib 300 mg Once Daily	Substudy 1: Cohort 1.3 Derazantinib 200 mg Twice Daily	Subst.2: Derazantinib 200 mg +Paclitaxel+ Ramucirumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	8	13	6
Units: Counts of participants				
number (not applicable)				
Unrelated TEAEs of Grade 3 or above	9	3	5	1
Related TEAEs of Grade 3 or above	0	3	6	4
No TEAEs of Grade 3 or above	4	2	2	1

End point values	Subst. 2: Derazantinib 300 / 400 mg +Paclitaxel+ Ramucirumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: Counts of participants				
number (not applicable)				
Unrelated TEAEs of Grade 3 or above	1			
Related TEAEs of Grade 3 or above	6			
No TEAEs of Grade 3 or above	0			

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	SS1 - C1.1 - DZB 300mg
Reporting group description:	
SS1 - C1.1 - DZB 300 mg	
Reporting group title	SS1 - C1.2 - DZB 300mg
Reporting group description:	
SS1 - C1.2 - DZB 300 mg	
Reporting group title	SS1 - C1.3 - DZB 200mg BID
Reporting group description:	
SS1 - C1.3 - DZB 200 mg BID	
Reporting group title	SS2 - DZB 200mg + RAM 8mg/kg + PAC 80mg/m2
Reporting group description:	
SS2 - DZB 200mg + RAM 8mg/kg + PAC 80mg/m2	
Reporting group title	SS2 - DZB 300mg + RAM 8mg/kg + PAC 80mg/m2
Reporting group description:	
SS2 - DZB 300mg + RAM 8mg/kg + PAC 80mg/m2	

Serious adverse events	SS1 - C1.1 - DZB 300mg	SS1 - C1.2 - DZB 300mg	SS1 - C1.3 - DZB 200mg BID
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 13 (53.85%)	4 / 8 (50.00%)	10 / 13 (76.92%)
number of deaths (all causes)	10	6	10
number of deaths resulting from adverse events	4	2	8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (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
Tumour pain			

subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (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
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (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
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	3 / 13 (23.08%)	2 / 8 (25.00%)	6 / 13 (46.15%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 6
General physical health deterioration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (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
Pyrexia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (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
Anal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (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
Stomatitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (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
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pulmonary embolism			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatic failure			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (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			
COVID-19 pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
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			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (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

Serious adverse events	SS2 - DZB 200mg + RAM 8mg/kg + PAC 80mg/m2	SS2 - DZB 300mg + RAM 8mg/kg + PAC 80mg/m2	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	3 / 7 (42.86%)	

number of deaths (all causes)	4	0	
number of deaths resulting from adverse events	3	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	3 / 6 (50.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	

General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertransaminasaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SS1 - C1.1 - DZB 300mg	SS1 - C1.2 - DZB 300mg	SS1 - C1.3 - DZB 200mg BID
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)	8 / 8 (100.00%)	13 / 13 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Colon cancer			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Thrombophlebitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Asthenia			
subjects affected / exposed	1 / 13 (7.69%)	4 / 8 (50.00%)	2 / 13 (15.38%)
occurrences (all)	1	4	2
Chills			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Fatigue			

subjects affected / exposed	2 / 13 (15.38%)	3 / 8 (37.50%)	5 / 13 (38.46%)
occurrences (all)	2	3	5
Feeling hot			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
General physical health deterioration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Mucosal inflammation			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oedema			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Reproductive system and breast disorders			
Bartholin's cyst			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Penile haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	2 / 8 (25.00%)	1 / 13 (7.69%)
occurrences (all)	0	3	1
Dyspnoea exertional			

subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pulmonary embolism			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 13 (15.38%)	2 / 8 (25.00%)	6 / 13 (46.15%)
occurrences (all)	2	2	6
Amylase increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 13 (15.38%)	2 / 8 (25.00%)	7 / 13 (53.85%)
occurrences (all)	2	2	9
Blood albumin decreased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	5 / 13 (38.46%)
occurrences (all)	1	1	5
Blood bilirubin increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Blood creatinine increased			

subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 13 (15.38%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	2	0	2
Blood glucose increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Blood phosphorus increased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
C-reactive protein increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood potassium increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neutrophil count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Lipase increased			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Platelet count increased			

subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Protein total decreased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Transaminases increased			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Weight decreased			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Weight increased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	2
Dysgeusia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Neuralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neuropathy peripheral			

subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neurotoxicity			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 13 (23.08%)	4 / 8 (50.00%)	4 / 13 (30.77%)
occurrences (all)	3	4	4
Lymphopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neutropenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Eyelid oedema			

subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dry eye			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Iridocyclitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Punctate keratitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Keratitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Visual impairment			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Abdominal pain upper			
subjects affected / exposed	3 / 13 (23.08%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	3	1	1
Abdominal pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	2 / 13 (15.38%)
occurrences (all)	0	2	2
Breath odour			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	5 / 13 (38.46%)
occurrences (all)	1	1	6

Constipation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	4 / 13 (30.77%)
occurrences (all)	1	0	4
Dry mouth			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	4 / 13 (30.77%)
occurrences (all)	0	1	4
Dysphagia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Erosive oesophagitis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Faeces discoloured			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Flatulence			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Melaena			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	5 / 13 (38.46%)	4 / 8 (50.00%)	6 / 13 (46.15%)
occurrences (all)	5	4	6

Odynophagia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Rectal haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	2 / 13 (15.38%)	3 / 8 (37.50%)	4 / 13 (30.77%)
occurrences (all)	2	3	4
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hepatic cytolysis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dry skin			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Nail dystrophy			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Onycholysis			

subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Pruritus			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Rash erythematous			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Skin toxicity			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Skin mass			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Muscular weakness			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Muscle haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Myalgia			

subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	3 / 13 (23.08%)
occurrences (all)	1	0	3
Pain in extremity			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
COVID-19			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Bronchitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gingivitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Respiratory tract infection viral			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 13 (7.69%)	2 / 8 (25.00%)	4 / 13 (30.77%)
occurrences (all)	1	2	5
Hyperglycaemia			

subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	0	1	1
Hyperphosphataemia			
subjects affected / exposed	3 / 13 (23.08%)	1 / 8 (12.50%)	1 / 13 (7.69%)
occurrences (all)	3	1	1
Hyperphosphatasaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hyperuricaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Hypoproteinaemia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hyponatraemia			
subjects affected / exposed	0 / 13 (0.00%)	1 / 8 (12.50%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 8 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	SS2 - DZB 200mg + RAM 8mg/kg + PAC 80mg/m2	SS2 - DZB 300mg + RAM 8mg/kg + PAC 80mg/m2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)	7 / 7 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Colon cancer			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Thrombophlebitis			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Asthenia			
subjects affected / exposed	1 / 6 (16.67%)	3 / 7 (42.86%)	
occurrences (all)	1	4	
Chills			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Feeling hot			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
General physical health deterioration			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Mucosal inflammation			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			

Bartholin's cyst			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Penile haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	2 / 6 (33.33%)	3 / 7 (42.86%)	
occurrences (all)	2	6	
Dyspnoea exertional			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Productive cough			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Insomnia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 6 (33.33%)	5 / 7 (71.43%)	
occurrences (all)	2	7	
Amylase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	

Aspartate aminotransferase increased				
subjects affected / exposed	3 / 6 (50.00%)	4 / 7 (57.14%)		
occurrences (all)	4	7		
Blood albumin decreased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)		
occurrences (all)	0	0		
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)		
occurrences (all)	1	3		
Blood bilirubin increased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)		
occurrences (all)	0	0		
Blood creatinine increased				
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)		
occurrences (all)	1	0		
Blood lactate dehydrogenase increased				
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)		
occurrences (all)	0	1		
Blood glucose increased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)		
occurrences (all)	0	0		
Blood phosphorus increased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)		
occurrences (all)	0	0		
C-reactive protein increased				
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)		
occurrences (all)	1	0		
Blood potassium increased				
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)		
occurrences (all)	0	0		
Electrocardiogram QT prolonged				
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)		
occurrences (all)	0	0		
Gamma-glutamyltransferase increased				

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Platelet count decreased			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	5	14	
Lipase increased			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Platelet count increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Protein total decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Transaminases increased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Weight increased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			

subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Dysgeusia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Neuralgia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Neuropathy peripheral			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	3	2	
Neurotoxicity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	13	
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 6 (50.00%)	3 / 7 (42.86%)	
occurrences (all)	5	5	
Lymphopenia			
subjects affected / exposed	2 / 6 (33.33%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	4 / 6 (66.67%)	5 / 7 (71.43%)	
occurrences (all)	5	15	

Thrombocytopenia			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Eyelid oedema			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Iridocyclitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Punctate keratitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Keratitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Visual impairment			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Abdominal distension			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Abdominal pain upper			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Breath odour			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 6 (33.33%)	2 / 7 (28.57%)	
occurrences (all)	2	5	
Constipation			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Dry mouth			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Dysphagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Erosive oesophagitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Faeces discoloured			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Flatulence			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Gastritis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Gingival swelling			

subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Melaena			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Haemorrhoids			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	1	2	
Odynophagia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	2	
Stomatitis			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	1	4	
Rectal haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	2	
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	3	
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Hepatic cytolysis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 6 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	3	
Dermatitis acneiform			

subjects affected / exposed	1 / 6 (16.67%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Nail disorder			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	1 / 6 (16.67%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Nail dystrophy			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Onycholysis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Rash erythematous			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Skin toxicity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Skin mass			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Back pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Muscular weakness			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Muscle haemorrhage			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Gingivitis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Hyperphosphataemia			
subjects affected / exposed	0 / 6 (0.00%)	2 / 7 (28.57%)	
occurrences (all)	0	4	
Hyperphosphatasaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Hyperuricaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Hypoproteinaemia			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hyponatraemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 December 2019	• Updated guidance on derazantinib dose reduction for management of toxicity in patients treated with derazantinib plus paclitaxel-ramucirumab in substudy 2. • Amended entry criteria to add a new Exclusion criterion 6 to exclude from the study patients with systolic blood pressure ≥ 150 mm Hg or diastolic ≥ 90 mm Hg. • Amended entry criteria to exclude from the planned (but not initiated) Substudy 3 patients who receive a live vaccine within 30 days prior to randomization. • Amended criteria for determination of RP2D and dose escalation in Substudy 2 to ensure that patients who received < 80% of the scheduled derazantinib, paclitaxel, or ramucirumab dose because of non-DLT toxicity were taken into consideration. • Amended study treatment description to ensure that in cohorts where paclitaxel is to be administered, co-administration of or premedication with drugs known to inhibit or induce either CYP2C8 or CYP3A4 was avoided. • Updated preparation procedures for atezolizumab (which was to have been used in the planned but not initiated Substudy 3). • Updated warnings, precautions and potential risks for derazantinib. • Biomarker and Patient Reported Outcome Manuals have been deleted from the protocol. • Proposed health economic assessment was deleted from the protocol.
13 March 2020	• The study title was amended. • Substudy 1 was amended to remove comparator treatment (paclitaxel-ramucirumab) and randomization, and to assign patients to cohorts based on type of FGFR GA. • Substudy 2 was amended to include only patients with FGFR GAs, and the number of patients to be enrolled in the expansion part of the study under the rules of the 3 + 3 design, and the decision making process for R2PD determination were clarified. • Secondary objectives that related to the pooling of randomized patient data from Substudy 1 and the planned (but not initiated) Substudy 3 were removed from Substudy 1 due to removal of randomization and comparator group from this substudy. • New non-clinical data were added to the study rationale. • Clarification of the composition and operation of the Independent Data Monitoring Committee. • Other changes affecting only Substudy 3, which was not initiated.

03 July 2020	• Transaminase elevations were removed from the list of potential risks for derazantinib, and upgraded to an identified risk. Phototoxicity was removed from the list of potential risks for derazantinib. The list of important potential risks for derazantinib was updated to include hyponatremia, and redefine 'creatinine increase' as 'blood creatinine increased / renal disorders'. • The list of adverse events of special interest was modified • Dose modification rules for ramucirumab in the event of proteinuria being observed were updated. • Patient eligibility criteria were revised for patients who would receive ramucirumab to more clearly reflect the Cyramza USPI and the Cyramza EPAR with respect to thrombotic and bleeding events. The eligibility criterion for Substudies in which atezolizumab was planned to be used were also modified to allow enrollment of patients with a chronic hepatitis B or hepatitis C infection, provided that these infections were not concurrent. • Revised definitions of potentially activating FGFRfus/amp/mt gene variants were implemented. • Screening procedures were amended so that sites at which local FGFR testing was performed as routine institutional practice were excepted from the requirement for a positive central FGFRfus/amp/mt test result prior to potentially study related assessments. • Anti-drug antibody analysis for ramucirumab was deleted from the exploratory endpoints. • Spot urine protein-creatinine ratio was added as an alternative test for the purposes of determining eligibility for the study in regard to urinary protein levels. • Administration of derazantinib with a light meal was permitted in the event of nausea or vomiting which is assessed as moderate. • Changes were made to the eligibility requirements for members of the Independent Data Monitoring Committee. • Translational Clinical Study groups and associated molecular analyses (in the planned but not initiated Substudy 3) were removed from the protocol.
21 March 2021	• Cohort 1.3 was introduced as a new cohort in patients with metastatic or recurrent locally advanced HER2neg FGFRfus/amp/mt GAC and radiologically confirmed disease progression after one or two standard treatment regimens. • Substudy 2 was amended to enroll approximately 32 patients with HER2neg FGFRfus/amp/mt GAC with radiologically confirmed disease progression after first-line standard treatment. •The design was modified to include a Phase-2-type Expansion Part, planned to enroll approximately 14 additional patients to ensure that approximately 20 efficacy-evaluable patients were dosed at the MTD, to support declaration of the RP2D and investigate the benefit-risk ratio of derazantinib-paclitaxel-ramucirumab. • The exclusion criterion referring to corneal or retinal disorder was revised to clarify that the disorder had to be clinically significant and likely to increase the risk of eye toxicity. • Exclusion criteria were amended to clarify the eligibility of patients with active/chronic hepatitis B and active hepatitis C. • A new exclusion criterion was added for patients with a serious or non healing wound, ulcer, or bone fracture. • A 90-day Safety Follow-up visit for all patients was added. • Positive FGFR1–3 GA test results obtained from local NGS testing of archival tissue isolated DNA, and/or RNA, and other liquid biopsy derived DNA for prospective patient enrolment were permitted in addition to central NGS testing. • Criteria for derazantinib dose reduction were amended. • The IDMC membership qualifications were amended. • Two additional changes related to atezolizumab-specific adverse events were also made (atezolizumab would have been used in the planned but not initiated Substudy 3).

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 in Substudy 2 could not be shown due to the restrictions of the EudraCT system;OS, DOR and PFS . The figures are on CT.gov: https://clinicaltrials.gov/study/NCT04604132

Notes: