



Clinical trial results:

A Multicenter, Randomized, Open-label, Phase 3 Trial Comparing Selpercatinib to Physicians Choice of Cabozantinib or Vandetanib in Patients with Progressive, Advanced, Kinase Inhibitor Naïve, RET-Mutant Medullary Thyroid Cancer (LIBRETTO-531)

Summary

EudraCT number	2019-001978-28
Trial protocol	CZ GB PL DE ES NL GR BE FR IT
Global end of trial date	

Results information

Result version number	v2 (current)
This version publication date	27 February 2025
First version publication date	05 June 2024
Version creation reason	<ul style="list-style-type: none">Correction of full data setRemoved crossover arm in AE section.

Trial information

Trial identification

Sponsor protocol code	J2G-MC-JZJB
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04211337
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 17478

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8005955979,

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	Interim
Date of interim/final analysis	22 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 May 2023
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare PFS of patients with progressive, advanced, kinase inhibitor naïve, RET-mutant MTC treated with selpercatinib versus cabozantinib or vandetanib.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 February 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	Netherlands: 9
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	France: 42
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	India: 11
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	China: 30
Country: Number of subjects enrolled	Taiwan: 5
Country: Number of subjects enrolled	Brazil: 33
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Australia: 11

Worldwide total number of subjects	291
EEA total number of subjects	132

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)	1
Adults (18-64 years)	215
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

If a participant has a recorded death on study, or is alive and being followed but off treatment, then the participant can be considered to be study completer.

Pre-assignment

Screening details:

Participants randomized to the Cabozantinib or Vandetanib arm will be allowed to crossover to receive the investigational product at the time of Blinded Independent Committee Review (BICR) confirmed radiographic progression.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Selpercatinib

Arm description:

160 milligrams (mg) Selpercatinib administered orally (PO) twice daily (BID).

Adolescent Dose: 92 milligrams per square meter (mg/m²) BID (not to exceed 160 mg BID).

Arm type	Experimental
Investigational medicinal product name	Selpercatinib
Investigational medicinal product code	LY3527723
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

160 mg Selpercatinib administered orally (PO) twice daily (BID).

Adolescent Dose: 92 mg/m² BID (not to exceed 160 mg BID).

Arm title	Cabozantinib or Vandetanib
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Arm description:

140 mg Cabozantinib administered orally daily (QD) or 300 mg Vandetanib administered orally QD per physician choice.

Cabozantinib Adolescent Dose: 40 mg/m².

Vandetanib Adolescent Dose:

- 0.7 - <0.9 - 100 mg every other day (QOD)
- 0.9 - <1.2 - 100 mg QD
- 1.2 - <1.6 - 7-day schedule 100 mg - 200 mg - 100 mg - 200 mg - 100 mg - 200 mg - 100 mg
- ≥1.6 - 200 QD

Arm type	Active comparator
Investigational medicinal product name	Cabozantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

140 mg Cabozantinib administered orally daily (QD)

Cabozantinib Adolescent Dose: 40 mg/m².

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

Dosage and administration details:

300 mg Vandetanib administered orally QD.

Vandetanib Adolescent Dose:

- 0.7 - <0.9 – 100 mg every other day (QOD)
- 0.9 - <1.2 – 100 mg QD
- 1.2 - <1.6 - 7-day schedule 100 mg - 200 mg - 100 mg - 200 mg - 100 mg - 200 mg - 100 mg
- ≥1.6 - 200 QD

Number of subjects in period 1	Selpercatinib	Cabozantinib or Vandetanib
Started	193	98
Received at Least One Dose of Study Drug	193	97
Completed	18	56
Not completed	175	42
On Treatment	175	40
Withdrawal by Subject	-	2

Baseline characteristics

Reporting groups

Reporting group title	Selpercatinib
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Reporting group description:

160 milligrams (mg) Selpercatinib administered orally (PO) twice daily (BID).

Adolescent Dose: 92 milligrams per square meter (mg/m²) BID (not to exceed 160 mg BID).

Reporting group title	Cabozantinib or Vandetanib
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Reporting group description:

140 mg Cabozantinib administered orally daily (QD) or 300 mg Vandetanib administered orally QD per physician choice.

Cabozantinib Adolescent Dose: 40 mg/m².

Vandetanib Adolescent Dose:

- 0.7 - <0.9 - 100 mg every other day (QOD)
- 0.9 - <1.2 - 100 mg QD
- 1.2 - <1.6 - 7-day schedule 100 mg - 200 mg - 100 mg - 200 mg - 100 mg - 200 mg - 100 mg
- ≥1.6 - 200 QD

Reporting group values	Selpercatinib	Cabozantinib or Vandetanib	Total
Number of subjects	193	98	291
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	1	0	1
Adults (18-64 years)	143	72	215
From 65-84 years	49	26	75
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	78	30	108
Male	115	68	183
Ethnicity			
Units: Subjects			
Hispanic or Latino	3	1	4
Not Hispanic or Latino	9	3	12
Unknown or Not Reported	181	94	275
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	43	24	67
Black or African American	5	2	7
White	116	52	168
More than one race	0	0	0
Unknown or Not Reported	29	20	49

Region of Enrollment			
Units: Subjects			
Netherlands	6	3	9
Poland	15	10	25
Spain	9	3	12
United Kingdom	9	3	12
Belgium	1	0	1
Czechia	6	0	6
France	24	18	42
Germany	7	6	13
Greece	3	1	4
Italy	14	6	20
United States	11	4	15
Japan	5	1	6
India	9	2	11
Canada	1	1	2
Korea, Republic of	10	2	12
China	14	16	30
Taiwan	4	1	5
Brazil	20	13	33
Israel	1	0	1
Russian Federation	15	6	21
Australia	9	2	11

End points

End points reporting groups

Reporting group title	Selpercatinib
Reporting group description: 160 milligrams (mg) Selpercatinib administered orally (PO) twice daily (BID). Adolescent Dose: 92 milligrams per square meter (mg/m ²) BID (not to exceed 160 mg BID).	
Reporting group title	Cabozantinib or Vandetanib
Reporting group description: 140 mg Cabozantinib administered orally daily (QD) or 300 mg Vandetanib administered orally QD per physician choice. Cabozantinib Adolescent Dose: 40 mg/m ² . Vandetanib Adolescent Dose: <ul style="list-style-type: none">• 0.7 - <0.9 - 100 mg every other day (QOD)• 0.9 - <1.2 - 100 mg QD• 1.2 - <1.6 - 7-day schedule 100 mg - 200 mg - 100 mg - 200 mg - 100 mg - 200 mg - 100 mg• ≥1.6 - 200 QD	

Primary: Progression Free Survival (PFS) by Blinded Independent Central Review (BICR)

End point title	Progression Free Survival (PFS) by Blinded Independent Central Review (BICR)
End point description: PFS is defined as the time from randomization until the occurrence of documented disease progression by the BICR, per Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria, or death from any cause in the absence of BICR-documented progressive disease. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, with reference being the smallest sum and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions. Analysis Population Description (APD): All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Censored participants: Selpercatinib - 167; Cabozantinib or Vandetanib - 66	
End point type	Primary
End point timeframe: Baseline to Progressive Disease or Death from Any Cause Up to 39 Months	

End point values	Selpercatinib	Cabozantinib or Vandetanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193 ^[1]	98		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	16.76 (12.22 to 25.10)		

Notes:

[1] - 9999 = Data unavailable due to high censoring.

Statistical analyses

Statistical analysis title	Selpercatinib, Cabozantinib or Vandetanib
Comparison groups	Cabozantinib or Vandetanib v Selpercatinib
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.165
upper limit	0.475

Notes:

[2] - Stratified by RET mutation type (M918T vs. Others) and intended treatment if randomized to Arm B (Vandetanib vs. Cabozantinib).

Secondary: Treatment Failure-Free Survival (TFFS) by Blinded Independent Committee Review (BICR)

End point title	Treatment Failure-Free Survival (TFFS) by Blinded Independent Committee Review (BICR)
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End point description:

TFFS by BICR is defined as the time from randomization to the first occurrence of documented radiographic disease progression per RECIST 1.1 as assessed by BICR; or unacceptable toxicity leading to treatment discontinuation as assessed by the investigator. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, with reference being the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions.

To qualify as an event, the toxicity must be from an intolerable AE (defined as any study drug-related AE that meets protocol guidance for treatment discontinuation, with the exception of alopecia); or death (due to any cause).

APD: All randomized participants, even if a participant did not take the assigned treatment.

End point type	Secondary
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End point timeframe:

Baseline to Progressive Disease, Unacceptable Toxicity or Death from Any Cause Up to 39 Months

End point values	Selpercatinib	Cabozantinib or Vandetanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193 ^[3]	98		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	13.93 (11.27 to 25.10)		

Notes:

[3] - 9999 = Data not available due to high censoring.

Statistical analyses

Statistical analysis title	Selpercatinib, Cabozantinib or Vandetanib
Comparison groups	Selpercatinib v Cabozantinib or Vandetanib
Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.254
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.153
upper limit	0.423

Notes:

[4] - Stratified by RET mutation type (M918T vs. Others) and intended treatment if randomized to Arm B (Vandetanib vs. Cabozantinib).

Secondary: Overall Response Rate (ORR): Percentage of Participants With Complete Response (CR) or Partial Response (PR) by BICR

End point title	Overall Response Rate (ORR): Percentage of Participants With Complete Response (CR) or Partial Response (PR) by BICR
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End point description:

ORR is defined as the number of participants who achieved the best overall response (BOR) of CR or PR divided by the total number of participants randomized to each treatment arm. ORR per RECIST 1.1 as assessed by BICR.

APD: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol.

End point type	Secondary
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End point timeframe:

Baseline through Disease Progression or Death up to 39 Months

End point values	Selpercatinib	Cabozantinib or Vandetanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	193	98		
Units: Percentage of participants				
number (confidence interval 95%)	69.4 (62.4 to 75.8)	38.8 (29.1 to 49.2)		

Statistical analyses

Statistical analysis title	Selpercatinib, Cabozantinib or Vandetanib
Comparison groups	Selpercatinib v Cabozantinib or Vandetanib

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[5]
Method	Clopper-Pearson Method
Parameter estimate	Odds ratio (OR)
Point estimate	3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.2
upper limit	6.3

Notes:

[5] - Stratified by RET mutation type (M918T vs. Others) and intended treatment if randomized to Arm B (Vandetanib vs. Cabozantinib).

Secondary: Duration of Response (DoR) by BICR

End point title	Duration of Response (DoR) by BICR
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End point description:

DoR by BICR is defined as the time from the date that measurement criteria for complete response (CR) or partial response (PR) (whichever is first recorded) are first met by the BICR or investigator assessment, as applicable, until the first date that disease is recurrent or documented disease progression is observed, per RECIST 1.1 criteria, or the date of death from any cause in the absence of documented disease progression or recurrence. Progressive Disease (PD) was at least a 20% increase in the sum of the diameters of target lesions, with reference being the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions.

APD: All randomized participants, even if a participant did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. Censored participants: Selpercatinib - 119, Cabozantinib or Vandetanib - 25

End point type	Secondary
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End point timeframe:

Date of CR or PR to Date of Disease Progression or Death Due to Any Cause Up to 39 Months

End point values	Selpercatinib	Cabozantinib or Vandetanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134 ^[6]	38 ^[7]		
Units: Months				
median (confidence interval 95%)	9999 (9999 to 9999)	16.56 (10.41 to 9999)		

Notes:

[6] - 9999 = Data not available due to high censoring.

[7] - 9999 = Data not available due to high censoring.

Statistical analyses

Statistical analysis title	Selpercatinib, Cabozantinib or Vandetanib
Comparison groups	Selpercatinib v Cabozantinib or Vandetanib

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 ^[8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.275
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.129
upper limit	0.587

Notes:

[8] - Stratified by RET mutation type (M918T vs. Others) and intended treatment if randomized to Arm B (Vandetanib vs. Cabozantinib).

Secondary: Comparative Tolerability: Number of Weeks With High Side Effect Bother Based Score of 3 or 4 on the Functional Assessment of Cancer Therapy Item GP5 (FACT-GP5)

End point title	Comparative Tolerability: Number of Weeks With High Side Effect Bother Based Score of 3 or 4 on the Functional Assessment of Cancer Therapy Item GP5 (FACT-GP5)
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End point description:

Comparative tolerability defined as a comparison of the proportion of time on treatment with high side effect bother as assessed by the FACT-GP5. The FACT-GP5 is a single question used to assess the overall bother of the treatment side effects. It is scored using a 5-point rating scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much), where lower scores reflect less bother from treatment side effects.

Time with high side effect bother (i.e.) score of 3 or 4 is reported here and was derived as follows: cumulative amount of time, in weeks, during which a participant reports high side effect bother divided by the total duration of therapy (weeks), derived as (date of last study treatment dose - date of first study treatment dose + 1) divided by 7.

APD: All participants who received the first dose of study treatment prior to the interim efficacy analysis and at least 6 months prior to the data cutoff date.

End point type	Secondary
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End point timeframe:

Baseline to Progressive Disease, Unacceptable Toxicity or Death from Any Cause Up to 39 Months

End point values	Selpercatinib	Cabozantinib or Vandetanib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	77		
Units: Weeks				
arithmetic mean (standard deviation)	0.08 (± 0.169)	0.24 (± 0.304)		

Statistical analyses

Statistical analysis title	Selpercatinib, Cabozantinib or Vandetanib
Comparison groups	Selpercatinib v Cabozantinib or Vandetanib

Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[9]
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	-0.1

Notes:

[9] - Stratified by RET mutation type (M918T vs. Others) and intended treatment if randomized to Arm B (Vandetanib vs. Cabozantinib).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 39 Months

Adverse event reporting additional description:

All randomized participants who received at least 1 dose (including a partial dose) of study treatment. Gender specific events occurring only in male or female participants have had the number of participants At Risk adjusted accordingly.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Selpercatinib - Treatment (TRT A)
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Reporting group description:

160 milligrams Selpercatinib administered orally (PO) twice daily (BID). Adolescent Dose: 92 milligrams per square meter (mg/m²) BID (not to exceed 160 mg BID).

Reporting group title	Cabozantinib or Vandetanib - Treatment B (TRT B)
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Reporting group description:

140 mg Cabozantinib administered orally daily (QD) or 300 mg Vandetanib administered orally QD per physician choice.

Cabozantinib Adolescent Dose: 40 mg/m².

Vandetanib Adolescent Dose:

0.7 - <0.9 - 100 mg every other day (QOD) 0.9 - <1.2 - 100 mg QD 1.2 - <1.6 - 7-day schedule 100 mg - 200 mg - 100 mg - 200 mg - 100 mg - 200 mg - 100 mg

≥1.6 - 200 QD

Serious adverse events	Selpercatinib - Treatment (TRT A)	Cabozantinib or Vandetanib - Treatment B (TRT B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 193 (22.28%)	27 / 97 (27.84%)	
number of deaths (all causes)	8	10	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
adenocarcinoma of colon			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
prostate cancer			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed ^[1]	1 / 115 (0.87%)	0 / 67 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectosigmoid cancer			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
squamous cell carcinoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
aortic stenosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemorrhage			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
hypertension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 193 (1.04%)	4 / 97 (4.12%)	
occurrences causally related to treatment / all	1 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
orthostatic hypotension			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (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			
colporrhaphy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed ^[2]	1 / 78 (1.28%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
inguinal hernia repair			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hip arthroplasty			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
proctectomy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
general physical health deterioration			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
fatigue			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
complication associated with device alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
pain alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
mucosal inflammation alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
multiple organ dysfunction syndrome alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		
pyrexia alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	3 / 193 (1.55%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	1 / 5	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
sudden death alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 1	0 / 0		

Reproductive system and breast disorders			
pelvic organ prolapse			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ovarian cyst			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed ^[3]	1 / 78 (1.28%)	0 / 30 (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			
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchostenosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dyspnoea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hiccups			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

lung disorder alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 193 (0.00%) 0 / 0 0 / 0	 1 / 97 (1.03%) 0 / 1 0 / 0	
pleural effusion alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 193 (0.52%) 2 / 2 0 / 0	 0 / 97 (0.00%) 0 / 0 0 / 0	
Psychiatric disorders suicidal ideation alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 193 (0.00%) 0 / 0 0 / 0	 1 / 97 (1.03%) 1 / 1 0 / 0	
Product issues device occlusion alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 193 (0.52%) 0 / 1 0 / 0	 0 / 97 (0.00%) 0 / 0 0 / 0	
Investigations blood sodium decreased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 0 / 193 (0.00%) 0 / 0 0 / 0	 1 / 97 (1.03%) 1 / 1 0 / 0	
blood bilirubin increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	 1 / 193 (0.52%) 0 / 1 0 / 0	 0 / 97 (0.00%) 0 / 0 0 / 0	
fibrin d dimer increased			

alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lipase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
liver function test increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
femur fracture			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
head injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
cardiac failure			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
intracranial pressure increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ischaemic stroke			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar radiculopathy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
motor dysfunction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
posterior reversible encephalopathy syndrome			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
seizure			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
polycythaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
retinopathy			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
colitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
anal cyst			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
gastritis				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
enteritis				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	1 / 97 (1.03%)		
occurrences causally related to treatment / all	1 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
diarrhoea				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
haemorrhoidal haemorrhage				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
inguinal hernia				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
large intestinal obstruction				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		

pancreatitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 193 (0.00%) 0 / 0 0 / 0	2 / 97 (2.06%) 1 / 2 0 / 0		
nausea alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 193 (0.52%) 0 / 1 0 / 0	1 / 97 (1.03%) 1 / 2 0 / 0		
oesophagitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 193 (0.52%) 0 / 1 0 / 0	0 / 97 (0.00%) 0 / 0 0 / 0		
vomiting alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 193 (0.00%) 0 / 0 0 / 0	1 / 97 (1.03%) 2 / 3 0 / 0		
Hepatobiliary disorders cholecystitis acute alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 193 (0.00%) 0 / 0 0 / 0	1 / 97 (1.03%) 0 / 1 0 / 0		
cholangitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 193 (0.00%) 0 / 0 0 / 0	1 / 97 (1.03%) 0 / 1 0 / 1		
drug-induced liver injury alternative dictionary used: MedDRA 26.0				

subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
jaundice			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
liver injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hepatic function abnormal			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
erythema multiforme			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hydronephrosis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
adrenocortical insufficiency acute			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
adrenal insufficiency			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypothyroidism			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
haemarthrosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteonecrosis of jaw			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteonecrosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (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			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
covid-19			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
gastroenteritis escherichia coli			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
gastroenteritis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
dengue fever				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
hepatitis viral				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
pneumonia				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	3 / 193 (1.55%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 3	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
peritonitis bacterial				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
urinary tract infection				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	2 / 193 (1.04%)	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
urosepsis				
alternative dictionary used: MedDRA 26.0				
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (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			
diabetic ketoacidosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
dehydration			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypercalcaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 193 (0.52%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypocalcaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypokalaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 193 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Gender specific events occurring only in male or female participants have had the number of participants At Risk adjusted accordingly.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Gender specific events occurring only in male or female participants have had the number of participants At Risk adjusted accordingly.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: Gender specific events occurring only in male or female participants have had the number of participants At Risk adjusted accordingly.

Non-serious adverse events	Selpercatinib - Treatment (TRT A)	Cabozantinib or Vandetanib - Treatment B (TRT B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	184 / 193 (95.34%)	96 / 97 (98.97%)	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	82 / 193 (42.49%)	39 / 97 (40.21%)	
occurrences (all)	158	76	
General disorders and administration site conditions			
face oedema			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	15 / 193 (7.77%)	2 / 97 (2.06%)	
occurrences (all)	19	3	
asthenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	21 / 193 (10.88%)	24 / 97 (24.74%)	
occurrences (all)	31	40	
fatigue			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	36 / 193 (18.65%)	20 / 97 (20.62%)	
occurrences (all)	61	43	
mucosal inflammation			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	14 / 193 (7.25%)	25 / 97 (25.77%)	
occurrences (all)	17	79	
oedema peripheral			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	32 / 193 (16.58%)	2 / 97 (2.06%)	
occurrences (all)	42	2	
pyrexia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	22 / 193 (11.40%)	2 / 97 (2.06%)	
occurrences (all)	29	2	
pain			

alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 8	6 / 97 (6.19%) 9	
Reproductive system and breast disorders erectile dysfunction alternative dictionary used: MedDRA 26.0 subjects affected / exposed ^[4] occurrences (all)	12 / 115 (10.43%) 15	0 / 67 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders cough alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) dysphonia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) dyspnoea alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) epistaxis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all) oropharyngeal pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	18 / 193 (9.33%) 25 3 / 193 (1.55%) 3 9 / 193 (4.66%) 11 8 / 193 (4.15%) 17 6 / 193 (3.11%) 8	7 / 97 (7.22%) 8 5 / 97 (5.15%) 7 5 / 97 (5.15%) 8 5 / 97 (5.15%) 7 6 / 97 (6.19%) 8	
Psychiatric disorders insomnia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	6 / 193 (3.11%) 10	5 / 97 (5.15%) 5	

Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	51 / 193 (26.42%)	33 / 97 (34.02%)	
occurrences (all)	139	57	
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	26 / 193 (13.47%)	13 / 97 (13.40%)	
occurrences (all)	67	22	
blood thyroid stimulating hormone increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	13 / 193 (6.74%)	13 / 97 (13.40%)	
occurrences (all)	16	14	
blood lactate dehydrogenase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 193 (4.66%)	14 / 97 (14.43%)	
occurrences (all)	11	17	
blood creatinine increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	18 / 193 (9.33%)	2 / 97 (2.06%)	
occurrences (all)	41	4	
blood bilirubin increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	21 / 193 (10.88%)	8 / 97 (8.25%)	
occurrences (all)	47	12	
blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	19 / 193 (9.84%)	13 / 97 (13.40%)	
occurrences (all)	37	16	
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	46 / 193 (23.83%)	37 / 97 (38.14%)	
occurrences (all)	105	60	
neutrophil count decreased			

<p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 193 (5.18%)</p> <p>24</p>	<p>9 / 97 (9.28%)</p> <p>22</p>	
<p>white blood cell count decreased</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>17 / 193 (8.81%)</p> <p>33</p>	<p>9 / 97 (9.28%)</p> <p>21</p>	
<p>platelet count decreased</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 193 (6.22%)</p> <p>16</p>	<p>7 / 97 (7.22%)</p> <p>17</p>	
<p>weight decreased</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 193 (5.18%)</p> <p>10</p>	<p>27 / 97 (27.84%)</p> <p>49</p>	
<p>weight increased</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>22 / 193 (11.40%)</p> <p>44</p>	<p>2 / 97 (2.06%)</p> <p>2</p>	
<p>Nervous system disorders</p> <p>dizziness</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>dysgeusia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>headache</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>paraesthesia</p> <p>alternative dictionary used: MedDRA 26.0</p>	<p>11 / 193 (5.70%)</p> <p>13</p> <p>10 / 193 (5.18%)</p> <p>10</p> <p>44 / 193 (22.80%)</p> <p>70</p>	<p>10 / 97 (10.31%)</p> <p>15</p> <p>16 / 97 (16.49%)</p> <p>19</p> <p>20 / 97 (20.62%)</p> <p>22</p>	

subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 6	7 / 97 (7.22%) 7	
Blood and lymphatic system disorders			
anaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	11 / 193 (5.70%) 12	10 / 97 (10.31%) 16	
leukopenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 13	6 / 97 (6.19%) 7	
lymphopenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 16	4 / 97 (4.12%) 4	
neutropenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 6	8 / 97 (8.25%) 17	
thrombocytopenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 5	9 / 97 (9.28%) 10	
Gastrointestinal disorders			
abdominal pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	19 / 193 (9.84%) 28	14 / 97 (14.43%) 30	
abdominal distension alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 16	2 / 97 (2.06%) 2	
ascites alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	11 / 193 (5.70%)	0 / 97 (0.00%)
occurrences (all)	11	0
abdominal pain upper		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	16 / 193 (8.29%)	7 / 97 (7.22%)
occurrences (all)	19	12
constipation		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	31 / 193 (16.06%)	12 / 97 (12.37%)
occurrences (all)	58	14
diarrhoea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	51 / 193 (26.42%)	59 / 97 (60.82%)
occurrences (all)	116	195
dry mouth		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	61 / 193 (31.61%)	10 / 97 (10.31%)
occurrences (all)	72	12
dyspepsia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	19 / 193 (9.84%)	8 / 97 (8.25%)
occurrences (all)	21	14
dysphagia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	6 / 193 (3.11%)	6 / 97 (6.19%)
occurrences (all)	7	7
gastrooesophageal reflux disease		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	8 / 193 (4.15%)	8 / 97 (8.25%)
occurrences (all)	11	11
nausea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	20 / 193 (10.36%)	31 / 97 (31.96%)
occurrences (all)	36	54

oral pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 3	5 / 97 (5.15%) 11	
stomatitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	7 / 193 (3.63%) 8	15 / 97 (15.46%) 32	
toothache alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	3 / 193 (1.55%) 4	5 / 97 (5.15%) 5	
vomiting alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	15 / 193 (7.77%) 20	20 / 97 (20.62%) 25	
Hepatobiliary disorders hepatic cytolysis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	5 / 193 (2.59%) 10	5 / 97 (5.15%) 7	
Skin and subcutaneous tissue disorders alopecia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 193 (5.18%) 10	7 / 97 (7.22%) 7	
acne alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	4 / 193 (2.07%) 5	6 / 97 (6.19%) 6	
dermatitis acneiform alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	1 / 193 (0.52%) 1	7 / 97 (7.22%) 8	
dry skin			

<p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>13 / 193 (6.74%)</p> <p>16</p>	<p>11 / 97 (11.34%)</p> <p>11</p>	
<p>hair colour changes</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 193 (0.00%)</p> <p>0</p>	<p>7 / 97 (7.22%)</p> <p>10</p>	
<p>palmar-plantar erythrodysaesthesia syndrome</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 193 (3.63%)</p> <p>7</p>	<p>41 / 97 (42.27%)</p> <p>93</p>	
<p>pruritus</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 193 (3.63%)</p> <p>9</p>	<p>5 / 97 (5.15%)</p> <p>6</p>	
<p>rash</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>28 / 193 (14.51%)</p> <p>36</p>	<p>20 / 97 (20.62%)</p> <p>39</p>	
<p>Renal and urinary disorders</p> <p>haematuria</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 193 (0.52%)</p> <p>1</p>	<p>8 / 97 (8.25%)</p> <p>13</p>	
<p>proteinuria</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>3 / 193 (1.55%)</p> <p>3</p>	<p>23 / 97 (23.71%)</p> <p>44</p>	
<p>Endocrine disorders</p> <p>hypothyroidism</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>12 / 193 (6.22%)</p> <p>18</p>	<p>4 / 97 (4.12%)</p> <p>4</p>	
<p>Musculoskeletal and connective tissue disorders</p>			

<p>arthralgia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>15 / 193 (7.77%)</p> <p>16</p>	<p>12 / 97 (12.37%)</p> <p>16</p>	
<p>back pain</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>12 / 193 (6.22%)</p> <p>18</p>	<p>11 / 97 (11.34%)</p> <p>11</p>	
<p>myalgia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>7 / 193 (3.63%)</p> <p>8</p>	<p>5 / 97 (5.15%)</p> <p>8</p>	
<p>neck pain</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>0 / 193 (0.00%)</p> <p>0</p>	<p>8 / 97 (8.25%)</p> <p>10</p>	
<p>pain in extremity</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>12 / 193 (6.22%)</p> <p>19</p>	<p>5 / 97 (5.15%)</p> <p>6</p>	
<p>Infections and infestations</p> <p>covid-19</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>19 / 193 (9.84%)</p> <p>19</p>	<p>17 / 97 (17.53%)</p> <p>17</p>	
<p>urinary tract infection</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>11 / 193 (5.70%)</p> <p>13</p>	<p>8 / 97 (8.25%)</p> <p>11</p>	
<p>Metabolism and nutrition disorders</p> <p>decreased appetite</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>23 / 193 (11.92%)</p> <p>29</p>	<p>27 / 97 (27.84%)</p> <p>45</p>	
<p>hypercalcaemia</p>			

alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 193 (5.18%)	0 / 97 (0.00%)	
occurrences (all)	22	0	
hyperphosphataemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	13 / 193 (6.74%)	2 / 97 (2.06%)	
occurrences (all)	21	2	
hypocalcaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	20 / 193 (10.36%)	25 / 97 (25.77%)	
occurrences (all)	43	56	
hypokalaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 193 (5.18%)	15 / 97 (15.46%)	
occurrences (all)	16	33	
hypomagnesaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 193 (5.18%)	7 / 97 (7.22%)	
occurrences (all)	15	13	
hyponatraemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	10 / 193 (5.18%)	4 / 97 (4.12%)	
occurrences (all)	24	5	

Notes:

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Gender specific events occurring only in male or female participants have had the number of participants At Risk adjusted accordingly.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2019	Amendment (a): Overall rationale for this amendment was to add information for adolescent such as dose and growth plate imaging. Additional information on AE collection and benefit/risk, dose modifications if hypersensitivity occurs. Modifications to inclusion/exclusion criteria per regulatory feedback.
18 November 2019	Amendment (b): Added the starting dose for the control arm treatment vandetanib for patients with mild to moderate renal impairment is incorporated, in order to maximize patient safety
10 June 2020	Amendment (c): There are two major changes within this amendment: <ul style="list-style-type: none">- Changing of the criteria of events counted toward the primary endpoint of treatment failure free survival (TFFS), and- Aligning the required visit schedule and procedures to better align with standard of care treatment with prolonged use of oral kinase inhibitors
15 February 2021	Amendment (d): The primary rationale for this amendment was to update information around the comparative tolerability key secondary objective based on regulatory agency feedback. Changes from additional regulatory and investigator feedback and minor corrections are also incorporated
04 November 2021	Amendment (e): In this amendment, the following changes are incorporated in response to: <ul style="list-style-type: none">- Regulatory feedback: Added progression free survival (PFS), as a primary endpoint and removed it as a secondary endpoint; Removed treatment failure free survival (TFFS), as a primary endpoint and added it as a secondary endpoint;- New external data disclosure: The study has been updated to an adaptive design to allow sample size re-estimation based on results at an interim analysis- Site feedback: Updated the cycles to align the visits with the schedule
06 April 2022	Amendment (f): Overall rationale for this amendment is in response to fluctuating vandetanib availability to ensure participants on control arm remain on active treatment. This amendment provides guidance to allow patients on vandetanib to switch to cabozantinib if necessary.
11 August 2023	Amendment (i): The primary purpose of this amendment is to update as per the latest Investigator Brochure (IB) and to align with EU Clinical Trial Regulation (EU-CTR) requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported