



Clinical trial results:

PHASE 1 STUDY TO COMPARE BEMPEGALDESLEUKIN COMBINED WITH NIVOLUMAB AND TYROSINE KINASE INHIBITOR (TKI) TO NIVOLUMAB AND TKI ALONE IN PARTICIPANTS WITH PREVIOUSLY UNTREATED ADVANCED OR METASTATIC RENAL CELL CARCINOMA (MRCC) (PIVOT IO 011)

Summary

EudraCT number	2018-003200-39
Trial protocol	FR ES DE
Global end of trial date	18 January 2024

Results information

Result version number	v1 (current)
This version publication date	18 January 2025
First version publication date	18 January 2025

Trial information

Trial identification

Sponsor protocol code	CA045-011
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb International Corporation
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com

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	18 January 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 January 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate safety, tolerability, DLTs, and RP2D of nivolumab, bempegaldesleukin, and axitinib combination.

To evaluate safety, tolerability, DLTs, and RP2D of nivolumab, bempegaldesleukin, and cabozantinib combination.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 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	Canada: 2
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	30
EEA total number of subjects	0

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)	23
From 65 to 84 years	7

85 years and over	0
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

30 subjects enrolled and treated

Period 1

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

Arms

Are arms mutually exclusive?	Yes
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Arm title	Part 1A: Treatment 1
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Arm description:

Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 5 mg Oral BID

Arm type	Experimental
Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

100 mg (10 mg/mL)

Investigational medicinal product name	bempedaldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use

Dosage and administration details:

1 mg of rhIL-2 per vial

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

Dosage and administration details:

1 mg, 5 mg or various strengths

Arm title	Part 1A: Treatment 2
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Arm description:

Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 3 mg Oral BID

Arm type	Experimental
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Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use
Dosage and administration details: 100 mg (10 mg/mL)	
Investigational medicinal product name	axitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 1 mg, 5 mg or various strengths	
Investigational medicinal product name	bempegaldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use
Dosage and administration details: 1 mg of rhIL-2 per vial	
Arm title	Part 1B: Treatment 1
Arm description: Nivolumab 360 mg IV Q3W + bempegaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 40mg Oral QD	
Arm type	Experimental
Investigational medicinal product name	cabozantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 20 mg, 40 mg or various strengths	
Investigational medicinal product name	bempegaldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use
Dosage and administration details: 1 mg of rhIL-2 per vial	
Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use
Dosage and administration details: 100 mg (10 mg/mL)	
Arm title	Part 1B: Treatment 2
Arm description: Nivolumab 360 mg IV Q3W + bempegaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 20mg Oral QD	

Arm type	Experimental
Investigational medicinal product name	nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use
Dosage and administration details: 100 mg (10 mg/mL)	
Investigational medicinal product name	cabozantinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 20 mg, 40 mg or various strengths	
Investigational medicinal product name	bempegaldesleukin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravascular use
Dosage and administration details: 1 mg of rhIL-2 per vial	

Number of subjects in period 1	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1
Started	7	8	7
Completed	0	0	0
Not completed	7	8	7
Consent withdrawn by subject	-	-	-
Other Reasons	-	-	7
Death	1	3	-
Follow-up no longer required per protocol	6	5	-

Number of subjects in period 1	Part 1B: Treatment 2
Started	8
Completed	0
Not completed	8
Consent withdrawn by subject	1
Other Reasons	1
Death	-
Follow-up no longer required per protocol	6

Baseline characteristics

Reporting groups

Reporting group title	Part 1A: Treatment 1
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 5 mg Oral BID	
Reporting group title	Part 1A: Treatment 2
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 3 mg Oral BID	
Reporting group title	Part 1B: Treatment 1
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 40mg Oral QD	
Reporting group title	Part 1B: Treatment 2
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 20mg Oral QD	

Reporting group values	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1
Number of subjects	7	8	7
Age Categorical Units: Participants			
Adults (18-64 years)	5	7	4
From 65-84 years	2	1	3
Age Continuous Units: years			
arithmetic mean	58.7	57.0	63.4
standard deviation	± 16.16	± 7.67	± 6.58
Sex: Female, Male Units: Participants			
Female	1	2	2
Male	6	6	5
Race Units: Subjects			
White	6	8	7
Black or African American	1	0	0
Other	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	0	0
Not Hispanic or Latino	6	8	7
Not Reported	0	0	0
Reporting group values	Part 1B: Treatment 2	Total	
Number of subjects	8	30	

Age Categorical			
Units: Participants			
Adults (18-64 years)	7	23	
From 65-84 years	1	7	
Age Continuous			
Units: years			
arithmetic mean	59.5		
standard deviation	± 6.50	-	
Sex: Female, Male			
Units: Participants			
Female	1	6	
Male	7	24	
Race			
Units: Subjects			
White	7	28	
Black or African American	0	1	
Other	1	1	
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	1	
Not Hispanic or Latino	7	28	
Not Reported	1	1	

End points

End points reporting groups

Reporting group title	Part 1A: Treatment 1
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 5 mg Oral BID	
Reporting group title	Part 1A: Treatment 2
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 3 mg Oral BID	
Reporting group title	Part 1B: Treatment 1
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 40mg Oral QD	
Reporting group title	Part 1B: Treatment 2
Reporting group description: Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 20mg Oral QD	

Primary: Number of Subjects with Adverse Events

End point title	Number of Subjects with Adverse Events ^[1]
End point description: Number of Subjects with Adverse Events. An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study treatment and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment. Here "99999" represents NA	
End point type	Primary
End point timeframe: From first dose to 100 days post last dose (Approximately 27 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: No Statistical Analysis for this endpoint

End point values	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1	Part 1B: Treatment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	8
Units: Subjects				
Any Grade	7	8	7	8
Grade 3 to 4	99999	99999	99999	99999

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Serious Adverse Events

End point title	Number of Subjects with Serious Adverse Events ^[2]
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End point description:

Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death if it were more severe).

End point type	Primary
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End point timeframe:

From first dose to 100 days post last dose (Approximately 27 months)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No Statistical Analysis for this endpoint

End point values	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1	Part 1B: Treatment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	8
Units: Subjects				
Any Grade	4	3	1	5
Grade 3 to 4	4	3	1	4

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with DLTs

End point title	Number of Subjects with DLTs ^[3]
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End point description:

DLTs will be defined based on the incidence, severity, and duration of AEs, for which no clear alternative cause is identified and that occur within the DLT window of 21 days from initiation of study drug(s). AEs will be graded according to the NCI CTCAE v5. For the purpose of participant management, potential DLTs that occur at any time, whether during dose escalation or after, will result in all study drug(s) being held pending evaluation of the event's relatedness to study drug, severity and duration.

End point type	Primary
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End point timeframe:

From first dose to 100 days post last dose (Approximately 25 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: No Statistical Analysis for this endpoint

End point values	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1	Part 1B: Treatment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	8
Units: Subjects	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with AEs leading to discontinuation

End point title	Number of Subjects with AEs leading to discontinuation ^[4]
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End point description:

Number of Subjects with AEs leading to discontinuation

End point type	Primary
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End point timeframe:

From first dose to 100 days post last dose (Approximately 27 months)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No Statistical Analysis for this endpoint

End point values	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1	Part 1B: Treatment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	8
Units: Subjects				
Any Grade	2	3	1	4
Grade 3 to 4	1	2	0	3

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with immune-mediated AEs

End point title	Number of subjects with immune-mediated AEs ^[5]
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End point description:

Number of subjects with immune-mediated AEs

End point type	Primary
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End point timeframe:

From first dose to 100 days post last dose (Approximately 27 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: No Statistical Analysis for this endpoint

End point values	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1	Part 1B: Treatment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	8
Units: Subjects				
Any Grade	0	2	0	0
Grade 3 to 4	0	0	0	0
Grade 5	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Clinical Laboratory Abnormalities

End point title	Number of Subjects with Clinical Laboratory Abnormalities ^[6]
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End point description:

Number of Subjects with Clinical Laboratory Abnormalities

End point type	Primary
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End point timeframe:

From first dose to 100 days post last dose (Approximately 27 months)

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No Statistical Analysis for this endpoint

End point values	Part 1A: Treatment 1	Part 1A: Treatment 2	Part 1B: Treatment 1	Part 1B: Treatment 2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	8	7	8
Units: Subjects				
Hemoglobin Grade 0	1	4	0	4
Platelet Count Grade 0	7	7	7	6
Leukocytes Grade 0	7	8	6	6
Lymphocytes (Absolute) Grade 0	6	5	3	8
Absolute Neutrophil Count Grade 0	6	7	5	4
Alakaline Phosphatase Grade 0	4	5	4	5
Aspartate Aminotransferase Grade 0	4	7	3	4
Alanine Amino Transferase Grade 0	4	5	0	2
Bilirubin Total Grade 0	4	7	7	6
Creatine Grade 0	1	1	1	1
Hypernatremia Grade 0	6	8	7	8
Hyopnatremia Grade 0	2	3	3	4
Hyperkalemia Grade 0	5	6	6	7
Hypokalemia Grade 0	6	7	7	8
Hypercalcemia Grade 0	5	7	6	6
Hypocalcemia Grade 0	6	6	7	7
Hypermagnesemia Grade 0	7	8	6	8
Hypomagnesemia Grade 0	6	7	5	8
Hypoglycemia Grade 0	7	7	7	6
Hemoglobin Grade 1	5	2	6	4

Platelet Count Grade 1	0	1	0	2
Leukocytes Grade 1	0	0	1	2
Lymphocytes (Absolute) Grade 1	1	2	2	0
Absolute Neutrophil Count Grade 1	1	0	2	2
Alakaline Phosphatase Grade 1	3	3	3	3
Aspartate Aminotransferase Grade 1	3	0	4	4
Alanine Amino Transferase Grade 1	3	2	7	5
Bilirubin Total Grade 1	2	1	0	2
Creatine Grade 1	4	5	5	7
Hypernatremia Grade 1	1	0	0	0
Hyopnatremia Grade 1	5	5	4	4
Hyperkalemia Grade 1	2	1	1	1
Hypokalemia Grade 1	1	1	0	0
Hypercalcemia Grade 1	1	1	1	2
Hypocalcemia Grade 1	1	2	0	1
Hypermagnesemia Grade 1	0	0	1	0
Hypomagnesemia Grade 1	1	1	2	0
Hypoglycemia Grade 1	0	1	0	2
Hemoglobin Grade 2	1	2	1	0
Platelet Count Grade 2	0	0	0	0
Leukocytes Grade 2	0	0	0	0
Lymphocytes (Absolute) Grade 2	0	0	1	0
Absolute Neutrophil Count Grade 2	0	0	0	1
Alakaline Phosphatase Grade 2	0	0	0	0
Aspartate Aminotransferase Grade 2	0	1	0	0
Alanine Amino Transferase Grade 2	0	0	0	1
Bilirubin Total Grade 2	1	0	0	0
Creatine Grade 2	2	2	1	0
Hypernatremia Grade 2	0	0	0	0
Hyopnatremia Grade 2	0	0	0	0
Hyperkalemia Grade 2	0	1	0	0
Hypokalemia Grade 2	0	0	0	0
Hypercalcemia Grade 2	1	0	0	0
Hypocalcemia Grade 2	0	0	0	0
Hypermagnesemia Grade 2	0	0	0	0
Hypomagnesemia Grade 2	0	0	0	0
Hypoglycemia Grade 2	0	0	0	0
Hemoglobin Grade 3	0	0	0	0
Platelet Count Grade 3	0	0	0	0
Leukocytes Grade 3	0	0	0	0
Lymphocytes (Absolute) Grade 3	0	1	1	0
Absolute Neutrophil Count Grade 3	0	1	0	1
Alakaline Phosphatase Grade 3	0	0	0	0
Aspartate Aminotransferase Grade 3	0	0	0	0
Alanine Amino Transferase Grade 3	0	1	0	0
Bilirubin Total Grade 3	0	0	0	0
Creatine Grade 3	0	0	0	0
Hypernatremia Grade 3	0	0	0	0
Hyopnatremia Grade 3	0	0	0	0
Hyperkalemia Grade 3	0	0	0	0
Hypokalemia Grade 3	0	0	0	0
Hypercalcemia Grade 3	0	0	0	0

Hypocalcemia Grade 3	0	0	0	0
Hypermagnesemia Grade 3	0	0	0	0
Hypomagnesemia Grade 3	0	0	0	0
Hypoglycemia Grade 3	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events and Serious Adverse Events: (From first dose to last dose + 100 days): Approximately 27 Months

All-Cause mortality (From randomization to end of study): Approximately 40 Months

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all Randomized Participants. The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	MedDRA26.1

Reporting groups

Reporting group title	Part 1A: Treatment 1
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Reporting group description:

Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 5 mg Oral BID

Reporting group title	Part 1B: Treatment 2
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Reporting group description:

Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 20mg Oral QD

Reporting group title	Part 1B: Treatment 1
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Reporting group description:

Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Cabozantinib 40mg Oral QD

Reporting group title	Part 1A: Treatment 2
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Reporting group description:

Nivolumab 360 mg IV Q3W + bempedaldesleukin 0.006 mg/kg IV Q3W combined with Axitinib 3 mg Oral BID

Serious adverse events	Part 1A: Treatment 1	Part 1B: Treatment 2	Part 1B: Treatment 1
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	5 / 8 (62.50%)	1 / 7 (14.29%)
number of deaths (all causes)	3	1	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (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
Vascular disorders			

Capillary leak syndrome			
subjects affected / exposed	0 / 7 (0.00%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal fistula			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			

subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (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
Haematochezia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (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
Haemoptysis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (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
Hypoxia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (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
Pulmonary embolism			
subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (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
Sepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 1A: Treatment 2		
Total subjects affected by serious adverse events			

subjects affected / exposed number of deaths (all causes) number of deaths resulting from adverse events	3 / 8 (37.50%) 3		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 8 (12.50%) 1 / 1 0 / 0		
Vascular disorders Capillary leak syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 8 (0.00%) 0 / 0 0 / 0		
Hypertension subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 8 (0.00%) 0 / 0 0 / 0		
Cardiac disorders Myocardial infarction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 8 (0.00%) 0 / 0 0 / 0		
Nervous system disorders Cerebrovascular accident subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 8 (0.00%) 0 / 0 0 / 0		
Syncope subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 8 (0.00%) 0 / 0 0 / 0		
Gastrointestinal disorders Gastrointestinal fistula			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Part 1A: Treatment 1	Part 1B: Treatment 2	Part 1B: Treatment 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	8 / 8 (100.00%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Breast neoplasm			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 7 (28.57%)	4 / 8 (50.00%)	3 / 7 (42.86%)
occurrences (all)	5	4	4
Hot flush			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Flushing			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pallor			

subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Hypotension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Chills			
subjects affected / exposed	2 / 7 (28.57%)	7 / 8 (87.50%)	2 / 7 (28.57%)
occurrences (all)	3	17	2
Chest discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Fatigue			
subjects affected / exposed	6 / 7 (85.71%)	6 / 8 (75.00%)	2 / 7 (28.57%)
occurrences (all)	7	10	2
Feeling of body temperature change			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Influenza like illness			
subjects affected / exposed	2 / 7 (28.57%)	3 / 8 (37.50%)	0 / 7 (0.00%)
occurrences (all)	3	9	0
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Oedema peripheral			
subjects affected / exposed	2 / 7 (28.57%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	3	1	1
Pain			

subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 10	4 / 8 (50.00%) 16	0 / 7 (0.00%) 0
Mucosal inflammation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Reproductive system and breast disorders Vulval disorder subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Pelvic pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	3 / 8 (37.50%) 3	0 / 7 (0.00%) 0
Asthma subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Dysphonia subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 4	2 / 8 (25.00%) 2	0 / 7 (0.00%) 0
Upper-airway cough syndrome subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Productive cough			

subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Pharyngeal ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Paranasal sinus hypersecretion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Haemoptysis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	3 / 7 (42.86%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Dyspnoea			
subjects affected / exposed	4 / 7 (57.14%)	2 / 8 (25.00%)	1 / 7 (14.29%)
occurrences (all)	6	2	1
Vocal cord thickening			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 7 (28.57%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Insomnia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	3	4	0
Depression			
subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0

Investigations			
Blood cholesterol increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	5 / 7 (71.43%)
occurrences (all)	1	1	5
Amylase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	3 / 7 (42.86%)
occurrences (all)	1	1	3
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	4 / 7 (57.14%)
occurrences (all)	0	0	4
Blood phosphorus decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Lipase increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 8 (12.50%) 1	1 / 7 (14.29%) 1
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Weight decreased subjects affected / exposed occurrences (all)	3 / 7 (42.86%) 3	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Weight increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Fall subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Infusion related reaction subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Thermal burn subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Cardiac disorders			
Aortic valve disease subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Coronary artery disease			

subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Bundle branch block right			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Brain fog			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Aphasia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Disturbance in attention			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 7 (28.57%)	4 / 8 (50.00%)	0 / 7 (0.00%)
occurrences (all)	3	6	0
Dizziness postural			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Dysgeusia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 7 (14.29%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Neuropathy peripheral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Migraine			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	5 / 7 (71.43%)	3 / 8 (37.50%)	1 / 7 (14.29%)
occurrences (all)	12	3	1
Peripheral motor neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Eosinophilia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Ear congestion			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tinnitus			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Vertigo subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Ear pruritus subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 2	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Eye disorders			
Dry eye subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Periorbital oedema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Periorbital swelling subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Vision blurred subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Visual impairment subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Gastrointestinal disorders			
Diverticulum subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Abdominal pain upper			

subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Constipation			
subjects affected / exposed	4 / 7 (57.14%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	7	1	1
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)	5 / 8 (62.50%)	2 / 7 (28.57%)
occurrences (all)	33	18	2
Abdominal discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Dyspepsia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	3	1	0
Enterocolitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gingival bleeding			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Glossitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Haematochezia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Hiatus hernia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Lip dry			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Mouth swelling			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	5 / 7 (71.43%)	6 / 8 (75.00%)	2 / 7 (28.57%)
occurrences (all)	19	12	2
Oral pain			
subjects affected / exposed	1 / 7 (14.29%)	3 / 8 (37.50%)	0 / 7 (0.00%)
occurrences (all)	1	4	0
Stomatitis			
subjects affected / exposed	5 / 7 (71.43%)	3 / 8 (37.50%)	2 / 7 (28.57%)
occurrences (all)	13	5	2
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	4 / 7 (57.14%)	5 / 8 (62.50%)	0 / 7 (0.00%)
occurrences (all)	16	11	0
Proctalgia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Alopecia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Blister			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	3 / 7 (42.86%)	3 / 8 (37.50%)	0 / 7 (0.00%)
occurrences (all)	7	5	0
Pruritus			
subjects affected / exposed	1 / 7 (14.29%)	5 / 8 (62.50%)	1 / 7 (14.29%)
occurrences (all)	1	9	1
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 7 (42.86%)	2 / 8 (25.00%)	1 / 7 (14.29%)
occurrences (all)	5	2	2
Night sweats			
subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Nail disorder			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hyperhidrosis			
subjects affected / exposed	1 / 7 (14.29%)	3 / 8 (37.50%)	0 / 7 (0.00%)
occurrences (all)	2	12	0
Eczema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Dermatitis acneiform			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Sensitive skin			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Rash maculo-papular subjects affected / exposed occurrences (all)	2 / 7 (28.57%) 2	1 / 8 (12.50%) 1	2 / 7 (28.57%) 2
Skin exfoliation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Renal and urinary disorders Urine abnormality subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Pollakiuria subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Nocturia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 8 (12.50%) 1	0 / 7 (0.00%) 0
Proteinuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Hypothyroidism subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	1 / 7 (14.29%) 1
Musculoskeletal and connective tissue disorders Flank pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	0 / 7 (0.00%) 0
Arthralgia subjects affected / exposed occurrences (all)	5 / 7 (71.43%) 6	3 / 8 (37.50%) 5	0 / 7 (0.00%) 0
Back pain			

subjects affected / exposed	2 / 7 (28.57%)	2 / 8 (25.00%)	1 / 7 (14.29%)
occurrences (all)	4	4	1
Musculoskeletal discomfort			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Muscular weakness			
subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Muscle tightness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 8 (25.00%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
COVID-19			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Diverticulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Furuncle			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Gingivitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Lower respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tooth infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Laryngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperlipidaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypercalcaemia			

subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Decreased appetite			
subjects affected / exposed	4 / 7 (57.14%)	2 / 8 (25.00%)	1 / 7 (14.29%)
occurrences (all)	9	4	1
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Hypophosphataemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1

Non-serious adverse events	Part 1A: Treatment 2		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Breast neoplasm			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	11		
Hot flush			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Flushing			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Embolism			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hypotension			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	4		
General disorders and administration site conditions			
Chills			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	21		
Chest discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Face oedema			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	5		
Fatigue			
subjects affected / exposed	8 / 8 (100.00%)		
occurrences (all)	29		
Feeling of body temperature change			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Localised oedema			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Non-cardiac chest pain			

<p>subjects affected / exposed</p> <p>0 / 8 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Oedema peripheral</p> <p>subjects affected / exposed</p> <p>4 / 8 (50.00%)</p> <p>occurrences (all)</p> <p>6</p>			
<p>Pain</p> <p>subjects affected / exposed</p> <p>2 / 8 (25.00%)</p> <p>occurrences (all)</p> <p>2</p>			
<p>Pyrexia</p> <p>subjects affected / exposed</p> <p>5 / 8 (62.50%)</p> <p>occurrences (all)</p> <p>29</p>			
<p>Mucosal inflammation</p> <p>subjects affected / exposed</p> <p>1 / 8 (12.50%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Immune system disorders</p> <p>Hypersensitivity</p> <p>subjects affected / exposed</p> <p>0 / 8 (0.00%)</p> <p>occurrences (all)</p> <p>0</p>			
<p>Reproductive system and breast disorders</p> <p>Vulval disorder</p> <p>subjects affected / exposed</p> <p>0 / 8 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Pelvic pain</p> <p>subjects affected / exposed</p> <p>1 / 8 (12.50%)</p> <p>occurrences (all)</p> <p>1</p>			
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>6 / 8 (75.00%)</p> <p>occurrences (all)</p> <p>10</p> <p>Asthma</p> <p>subjects affected / exposed</p> <p>0 / 8 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Dysphonia</p> <p>subjects affected / exposed</p> <p>4 / 8 (50.00%)</p> <p>occurrences (all)</p> <p>7</p> <p>Upper-airway cough syndrome</p>			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Pharyngeal ulceration			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Paranasal sinus hypersecretion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hiccups			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Haemoptysis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	6		
Vocal cord thickening			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

Insomnia			
subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	14		
Depression			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Investigations			
Blood cholesterol increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Alanine aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Amylase increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood creatinine increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood phosphorus decreased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Blood thyroid stimulating hormone			

increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Ejection fraction decreased subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Lipase increased subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Weight decreased subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 5		
Weight increased subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Fall subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2		
Infusion related reaction subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 5		
Procedural pain subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Thermal burn subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Cardiac disorders			

Aortic valve disease subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Supraventricular extrasystoles subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Coronary artery disease subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Sinus tachycardia subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 2		
Bundle branch block right subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Tachycardia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Nervous system disorders			
Brain fog subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Aphasia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Disturbance in attention subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Dizziness subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 3		
Dizziness postural subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Dysgeusia			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Neuropathy peripheral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hypoaesthesia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Headache			
subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	20		
Peripheral motor neuropathy			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Lymphadenopathy			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Eosinophilia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Deafness			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Ear congestion			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Ear pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vertigo			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Ear pruritus			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Periorbital oedema			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	2		
Periorbital swelling			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

Gastrointestinal disorders			
Diverticulum			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Abdominal pain			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	5		
Diarrhoea			
subjects affected / exposed	8 / 8 (100.00%)		
occurrences (all)	53		
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dry mouth			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	12		
Enterocolitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gingival bleeding			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Glossitis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hiatus hernia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lip dry			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Mouth swelling			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	7 / 8 (87.50%)		
occurrences (all)	27		
Oral pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Stomatitis			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	8		
Toothache			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Vomiting			

subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	11		
Proctalgia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Alopecia			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Blister			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	9		
Pruritus			
subjects affected / exposed	6 / 8 (75.00%)		
occurrences (all)	12		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	5		
Night sweats			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nail disorder			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Hyperhidrosis			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	11		
Eczema			

subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	6		
Dermatitis acneiform			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Sensitive skin			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Skin exfoliation			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Renal and urinary disorders			
Urine abnormality			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Nocturia			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Hypothyroidism			

subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Flank pain			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Arthralgia			
subjects affected / exposed	4 / 8 (50.00%)		
occurrences (all)	8		
Back pain			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Muscle tightness			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	5 / 8 (62.50%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	3 / 8 (37.50%)		
occurrences (all)	3		
Neck pain			

subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Infections and infestations			
Arthritis infective			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
COVID-19			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Diverticulitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Furuncle			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		
Gingivitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Sinusitis			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Tooth infection			
subjects affected / exposed	0 / 8 (0.00%)		
occurrences (all)	0		

Laryngitis subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Metabolism and nutrition disorders			
Hyperlipidaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Hypercalcaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Dehydration subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1		
Decreased appetite subjects affected / exposed occurrences (all)	6 / 8 (75.00%) 13		
Hyponatraemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		
Hypomagnesaemia subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 December 2020	Revision to align with study design modification that incorporated cabozantinib Modifications made to bridge bempegaldesleukin and nivolumab program updates to align with Common Terminology Criteria for Adverse Event (CTCAE) version 5 Incorporates Administrative Letter 01 Revision to inclusion criteria 2)h, 2)i, 3)h)iv through 3)h)vii; added exclusion criteria 1)x and 2)g Added SARS-CoV-2 language Updated Appendix 11 management algorithms
28 June 2022	Text was updated to discontinue treatment with bempegaldesleukin and may continue to receive nivolumab plus a tyrosine kinase inhibitor. The maximum study duration was shortened to the nivolumab treatment period (2 years) plus 100 days for safety follow-up. Imaging will be performed per standard of care. All study treatment decisions including progression and recurrence will be based on the Investigator's assessment of tumor images. All enrollment to the CA045011 study has stopped. As the Phase 2 enrollment will not be initiated, with this amendment the Part 2 (Phase 2) activities are not applicable.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported