



Clinical trial results:

A Phase 1/2, Open-label, Multicenter Study to Investigate the Safety and Preliminary Efficacy of Combined Bempegaldesleukin (NKTR-214) and Pembrolizumab with or without Chemotherapy in Patients with Locally Advanced or Metastatic Solid Tumors

Summary

EudraCT number	2019-003474-35
Trial protocol	DE ES IT
Global end of trial date	05 July 2022

Results information

Result version number	v1 (current)
This version publication date	29 December 2022
First version publication date	29 December 2022

Trial information

Trial identification

Sponsor protocol code	16-214-05
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03138889
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Nektar Therapeutics
Sponsor organisation address	455 Mission Bay Boulevard South, San Francisco, United States,
Public contact	Clinical Trial Information Desk, Nektar Therapeutics, +1 855 482 8676, studyinquiry@nektar.com
Scientific contact	Clinical Trial Information Desk, Nektar Therapeutics, +1 855 482 8676, studyinquiry@nektar.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	27 July 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 July 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

- To determine the ORR per blinded independent central review (BICR) by RECIST 1.1 of NKTR-214 plus pembrolizumab with or without systemic chemotherapy in patients with untreated metastatic NSCLC.

Protection of trial subjects:

A risk-based approach to management, monitoring, and oversight of the study was implemented, including:

- Proactive risk management, addressing areas of project risk in a prospective manner to allow for planning and prevention of negative risk, while taking advantage of pre-identified positive opportunities for improvement of project objectives. This included risk planning, risk identification, qualitative analysis of the risks, quantitative analysis of the risks, risk response, and risk monitoring and control, with risks tracked in the study Risk Register
- A risk-based approach to site monitoring, utilizing a combination of onsite and remote monitoring visits:
 - o A volume-based monitoring strategy was employed with volume-based ("milestone event") triggering of onsite monitoring visits at clinical sites. Examples of volume-based milestone events were: number of patients enrolled, number of data points entered into electronic data capture (EDC) and number of case report forms (CRFs) ready for Source Data Verification (SDV) at a clinical site. Remote monitoring visits were triggered at high-enrolling sites, those with significant issues, or data backlog related to queries and missing pages only, as well as at sites with less than 80% SDV, or as otherwise approved by Nektar.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 June 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 96
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	162
EEA total number of subjects	66

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)	74
From 65 to 84 years	87
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Please refer to "Subjects enrolled per country" section above.

Pre-assignment

Screening details:

Patients with select locally advanced or metastatic solid tumors and measurable disease per RECIST 1.1: first- and second-line melanoma, NSCLC, urothelial carcinoma, HNSCC, and HCC for the dose optimization; first-line NSCLC for the dose expansion; and second-line NSCLC and first- and second-line urothelial carcinoma for before protocol amendment 5

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 0 (Before Protocol Amendment 5.0)

Arm description:

Patients enrolled before Protocol Amendment 5.0

Arm type	Experimental
Investigational medicinal product name	NKTR-214
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous 0.006 mg/kg once every 3 weeks

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100 mg

Investigational medicinal product name	Atezolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1200 mg

Arm title	Cohort 1a (dose optimization)
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Arm description:

Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) were to start NKTR-214 at a dose of 0.008 mg/kg once every 3 weeks (q3w) with pembrolizumab.

Arm type	Experimental
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Investigational medicinal product name	NKTR-214
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous NKTR-214 0.008, 0.010, and 0.012 mg/kg once every 3 weeks	
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
100 mg	
Arm title	Cohort 2 (dose expansion)
Arm description:	
Patients were to receive a dose of 0.006 mg/kg of NKTR-214 combined with pembrolizumab.	
Arm type	Experimental
Investigational medicinal product name	NKTR-214
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous NKTR-214 0.006 mg/kg once every 3 weeks	
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
100 mg	
Arm title	Cohort 3 (dose expansion)
Arm description:	
Patients were to receive a starting at a dose of 0.010 mg/kg of NKTR-214 combined with pembrolizumab.	
Arm type	Experimental
Investigational medicinal product name	NKTR-214
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous NKTR-214 0.010 mg/kg once every 3 weeks	
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
100 mg	

Arm title	Cohort 4/5 (dose expansion)
Arm description:	
Following review of safety and efficacy data from Cohorts 2 and 3, a decision was to be made to initiate Cohorts 4 and 5. In Cohorts 4 and 5, patients were to receive 0.006 mg/kg of NKTR-214 combined with pembrolizumab and platinum-based chemotherapy.	
Arm type	Experimental
Investigational medicinal product name	NKTR-214
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
Intravenous NKTR-214 0.006 mg/kg once every 3 weeks	
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details:	
100 mg	

Number of subjects in period 1	Cohort 0 (Before Protocol Amendment 5.0)	Cohort 1a (dose optimization)	Cohort 2 (dose expansion)
Started	35	18	75
Completed	0	0	0
Not completed	35	18	75
Consent withdrawn by subject	10	3	3
Death	22	9	39
Sponsor decision	3	6	33

Number of subjects in period 1	Cohort 3 (dose expansion)	Cohort 4/5 (dose expansion)
Started	17	17
Completed	0	0
Not completed	17	17
Consent withdrawn by subject	-	1
Death	5	2
Sponsor decision	12	14

Baseline characteristics

Reporting groups

Reporting group title	Cohort 0 (Before Protocol Amendment 5.0)
Reporting group description:	
Patients enrolled before Protocol Amendment 5.0	
Reporting group title	Cohort 1a (dose optimization)
Reporting group description:	
Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) were to start NKTR-214 at a dose of 0.008 mg/kg once every 3 weeks (q3w) with pembrolizumab.	
Reporting group title	Cohort 2 (dose expansion)
Reporting group description:	
Patients were to receive a dose of 0.006 mg/kg of NKTR-214 combined with pembrolizumab.	
Reporting group title	Cohort 3 (dose expansion)
Reporting group description:	
Patients were to receive a starting at a dose of 0.010 mg/kg of NKTR-214 combined with pembrolizumab.	
Reporting group title	Cohort 4/5 (dose expansion)
Reporting group description:	
Following review of safety and efficacy data from Cohorts 2 and 3, a decision was to be made to initiate Cohorts 4 and 5. In Cohorts 4 and 5, patients were to receive 0.006 mg/kg of NKTR-214 combined with pembrolizumab and platinum-based chemotherapy.	

Reporting group values	Cohort 0 (Before Protocol Amendment 5.0)	Cohort 1a (dose optimization)	Cohort 2 (dose expansion)
Number of subjects	35	18	75
Age categorical			
Units: Subjects			
Adults (18-64 years)	16	8	35
From 65-84 years	18	10	40
85 years and over	1	0	0
Age continuous			
Units: years			
arithmetic mean	67.2	62.6	65.8
standard deviation	± 11.20	± 10.15	± 9.30
Gender categorical			
Units: Subjects			
Female	11	11	24
Male	24	7	51
Ethnicity			
Units: Subjects			
Hispanic or Latino	2	0	3
Not Hispanic or Latino	30	18	65
Not Reported	0	0	3
Unknown	3	0	4
Race			
Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	0	1	0
Black or African American	3	0	2

Native Hawaiian or Other Pacific Islander	0	0	0
White	31	17	72
Other	1	0	1
Not Reported	0	0	0
Eastern Cooperative Oncology Group Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Units: Subjects			
ECOG 0	18	10	33
ECOG 1	17	8	42
Smoking Status			
Units: Subjects			
Smoker	3	3	23
Past smoker	19	7	46
Non-smoker	13	8	6
Unknown	0	0	0
Height			
Units: centimeters			
arithmetic mean	171.6	171.5	169.4
standard deviation	± 11.94	± 11.42	± 9.38
Weight			
Units: kilograms			
arithmetic mean	86.7	79.2	73.6
standard deviation	± 17.36	± 24.53	± 15.87
Calculated Body Mass Index			
Units: kilogram(s)/square metre			
arithmetic mean	29.6	26.5	25.6
standard deviation	± 5.70	± 6.18	± 5.07

Reporting group values	Cohort 3 (dose expansion)	Cohort 4/5 (dose expansion)	Total
Number of subjects	17	17	162
Age categorical			
Units: Subjects			
Adults (18-64 years)	6	9	74
From 65-84 years	11	8	87
85 years and over	0	0	1
Age continuous			
Units: years			
arithmetic mean	67.9	61.1	
standard deviation	± 5.97	± 10.35	-
Gender categorical			
Units: Subjects			
Female	4	7	57
Male	13	10	105
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	0	5
Not Hispanic or Latino	17	14	144
Not Reported	0	1	4
Unknown	0	2	9
Race			

Units: Subjects			
American Indian or Alaskan Native	0	0	0
Asian	0	0	1
Black or African American	1	1	7
Native Hawaiian or Other Pacific Islander	0	0	0
White	16	15	151
Other	0	0	2
Not Reported	0	1	1
Eastern Cooperative Oncology Group Performance Status			
Eastern Cooperative Oncology Group (ECOG) Performance Status			
Units: Subjects			
ECOG 0	8	6	75
ECOG 1	9	11	87
Smoking Status			
Units: Subjects			
Smoker	3	2	34
Past smoker	11	13	96
Non-smoker	3	2	32
Unknown	0	0	0
Height			
Units: centimeters			
arithmetic mean	171.3	174.5	
standard deviation	± 8.30	± 10.64	-
Weight			
Units: kilograms			
arithmetic mean	74.3	78.7	
standard deviation	± 10.10	± 16.99	-
Calculated Body Mass Index			
Units: kilogram(s)/square metre			
arithmetic mean	25.3	25.9	
standard deviation	± 2.40	± 5.66	-

End points

End points reporting groups

Reporting group title	Cohort 0 (Before Protocol Amendment 5.0)
Reporting group description: Patients enrolled before Protocol Amendment 5.0	
Reporting group title	Cohort 1a (dose optimization)
Reporting group description: Patients enrolled in the 3 + 3 dose optimization schema (Cohort 1a) were to start NKTR-214 at a dose of 0.008 mg/kg once every 3 weeks (q3w) with pembrolizumab.	
Reporting group title	Cohort 2 (dose expansion)
Reporting group description: Patients were to receive a dose of 0.006 mg/kg of NKTR-214 combined with pembrolizumab.	
Reporting group title	Cohort 3 (dose expansion)
Reporting group description: Patients were to receive a starting at a dose of 0.010 mg/kg of NKTR-214 combined with pembrolizumab.	
Reporting group title	Cohort 4/5 (dose expansion)
Reporting group description: Following review of safety and efficacy data from Cohorts 2 and 3, a decision was to be made to initiate Cohorts 4 and 5. In Cohorts 4 and 5, patients were to receive 0.006 mg/kg of NKTR-214 combined with pembrolizumab and platinum-based chemotherapy.	
Subject analysis set title	Cohort 1a: NKTR-214 0.008 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who received NKTR-214 0.008 mg/kg every 3 weeks + pembrolizumab 200 mg in Cohort 1a.	
Subject analysis set title	Cohort 1a: NKTR-214 0.010 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who received NKTR-214 0.010 mg/kg every 3 weeks + pembrolizumab 200 mg in Cohort 1a.	
Subject analysis set title	Cohort 1a: NKTR-214 0.012 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients who received NKTR-214 0.012 mg/kg every 3 weeks + pembrolizumab 200 mg in Cohort 1a.	

Primary: Cohort 2: Objective Response Rate for Dose Expansion Cohorts - Objective Response

End point title	Cohort 2: Objective Response Rate for Dose Expansion Cohorts - Objective Response ^{[1][2]}
End point description: Objective Response Rate per blinded independent central review (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) for the Response Evaluable Population dose expansion Cohort 2. The Response Evaluable Population was subjects who received at least 1 dose (or partial dose) of study drug, had measurable disease (per RECIST 1.1) at baseline, and had at least 1 post-baseline assessment of tumor response. Objective response is the sum of confirmed complete response and confirmed partial response.	
End point type	Primary
End point timeframe: Until disease progression, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, patient withdrew consent or was lost to follow-up, or the study was terminated by the Sponsor; or until max 2 years.	

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: Not applicable.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoints are presented by individual cohort.

End point values	Cohort 2 (dose expansion)			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: participants	13			

Statistical analyses

No statistical analyses for this end point

Primary: Cohort 3: Objective Response Rate for Dose Expansion Cohorts - Objective Response

End point title	Cohort 3: Objective Response Rate for Dose Expansion Cohorts - Objective Response ^[3] ^[4]
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End point description:

Objective Response Rate per blinded independent central review (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) for the Response Evaluable Population dose expansion Cohort 3. The Response Evaluable Population was subjects who received at least 1 dose (or partial dose) of study drug, had measurable disease (per RECIST 1.1) at baseline, and had at least 1 post-baseline assessment of tumor response.

Objective response is the sum of confirmed complete response and confirmed partial response.

End point type	Primary
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End point timeframe:

Until disease progression, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, patient withdrew consent or was lost to follow-up, or the study was terminated by the Sponsor; or until max 2 years.

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: Not applicable.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoints are presented by individual cohort.

End point values	Cohort 3 (dose expansion)			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: participants	2			

Statistical analyses

No statistical analyses for this end point

Primary: Cohort 4+5: Primary Endpoint: Objective Response Rate for Dose Expansion Cohorts - Objective Response

End point title	Cohort 4+5: Primary Endpoint: Objective Response Rate for Dose Expansion Cohorts - Objective Response ^{[5][6]}
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End point description:

Objective Response Rate per blinded independent central review (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) for the Response Evaluable Population dose expansion Cohorts 4+5. The Response Evaluable Population was subjects who received at least 1 dose (or partial dose) of study drug, had measurable disease (per RECIST 1.1) at baseline, and had at least 1 post-baseline assessment of tumor response.

Objective response is the sum of confirmed complete response and confirmed partial response.

End point type	Primary
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End point timeframe:

Until disease progression, death, unacceptable toxicity, symptomatic deterioration, Investigator's decision to discontinue treatment, patient withdrew consent or was lost to follow-up, or the study was terminated by the Sponsor; or until max 2 years.

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: Not applicable.

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoints are presented by individual cohort.

End point values	Cohort 4/5 (dose expansion)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants	2			

Statistical analyses

No statistical analyses for this end point

Primary: Safety and tolerability of NKTR 214 in combination with pembrolizumab

End point title	Safety and tolerability of NKTR 214 in combination with pembrolizumab ^[7]
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End point description:

To evaluate the safety and tolerability of NKTR 214 in combination with pembrolizumab in Cohort 1a. The overall summary of treatment-emergent adverse events is presented for the Safety Population in dose optimization Cohort 1a.

DLT = dose limiting toxicity

End point type	Primary
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End point timeframe:

Screening (Days -28 to -1) to post-treatment period (end of treatment [30 days +/- 10 days after last dose of study medications or before new antineoplastic regimen starts], or long-term follow-up [until withdrawal of consent, death or study termination])

Notes:

[7] - 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: Not applicable.

End point values	Cohort 1a: NKTR-214 0.008 mg/kg	Cohort 1a: NKTR-214 0.010 mg/kg	Cohort 1a: NKTR-214 0.012 mg/kg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4	7	7	
Units: participants				
Patients reporting at least 1 DLT	0	1	0	
DLT: Hypotension (Vascular Disorder)	0	1	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening (Days -28 to -1) to post-treatment period (end of treatment [30 days +/- 10 days after last dose of study medications or before new antineoplastic regimen starts], or long-term follow-up [until withdrawal of consent, death or study termination])

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Before Protocol Amendment 5
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Reporting group description:

This group presents data for participants enrolled before protocol amendment 5.

Reporting group title	On or after Protocol Amendment 5 (Cohort 1a to 5)
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Reporting group description:

This group presents data for participants enrolled on or after protocol amendment 5.

Serious adverse events	Before Protocol Amendment 5	On or after Protocol Amendment 5 (Cohort 1a to 5)	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 35 (54.29%)	56 / 127 (44.09%)	
number of deaths (all causes)	22	56	
number of deaths resulting from adverse events	2	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion malignant			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour invasion			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 35 (2.86%)	3 / 127 (2.36%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chills			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 35 (0.00%)	4 / 127 (3.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			

subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (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			
Infusion related reaction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 35 (2.86%)	4 / 127 (3.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Embololic stroke			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenic syndrome			

subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolic cerebral infarction			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (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			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Tubulointerstitial nephritis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (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			
subjects affected / exposed	2 / 35 (5.71%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)	7 / 127 (5.51%)	
occurrences causally related to treatment / all	0 / 1	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Before Protocol Amendment 5	On or after Protocol Amendment 5 (Cohort 1a to 5)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 35 (100.00%)	124 / 127 (97.64%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Cancer pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Lung neoplasm malignant			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Melanocytic naevus subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Squamous cell carcinoma of skin subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Vascular disorders			
Hypotension subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	18 / 127 (14.17%) 23	
Hypertension subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 4	10 / 127 (7.87%) 11	
Hot flush subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	4 / 127 (3.15%) 4	
Embolism subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 127 (0.79%) 1	
Flushing subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 127 (0.79%) 1	
Lymphoedema subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 127 (0.79%) 1	
Arterial thrombosis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Deep vein thrombosis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Peripheral coldness subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	

Phlebitis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
superior vena			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Sinus operation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	10 / 35 (28.57%)	53 / 127 (41.73%)	
occurrences (all)	18	80	
Fatigue			
subjects affected / exposed	20 / 35 (57.14%)	42 / 127 (33.07%)	
occurrences (all)	24	52	
Chills			
subjects affected / exposed	6 / 35 (17.14%)	27 / 127 (21.26%)	
occurrences (all)	10	34	
Asthenia			
subjects affected / exposed	3 / 35 (8.57%)	28 / 127 (22.05%)	
occurrences (all)	3	38	
Influenza like illness			
subjects affected / exposed	7 / 35 (20.00%)	20 / 127 (15.75%)	
occurrences (all)	10	48	
Oedema peripheral			
subjects affected / exposed	9 / 35 (25.71%)	17 / 127 (13.39%)	
occurrences (all)	9	24	
Non-cardiac chest pain			
subjects affected / exposed	2 / 35 (5.71%)	7 / 127 (5.51%)	
occurrences (all)	2	9	
Gait disturbance			
subjects affected / exposed	2 / 35 (5.71%)	2 / 127 (1.57%)	
occurrences (all)	2	2	
Malaise			

subjects affected / exposed	3 / 35 (8.57%)	1 / 127 (0.79%)
occurrences (all)	14	1
Mucosal inflammation		
subjects affected / exposed	0 / 35 (0.00%)	4 / 127 (3.15%)
occurrences (all)	0	4
Catheter site pain		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	3
Face oedema		
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)
occurrences (all)	1	3
Pain		
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)
occurrences (all)	1	2
Localised oedema		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	3
Axillary pain		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Chest discomfort		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Chest pain		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Device occlusion		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	4
Feeling abnormal		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Infusion site extravasation		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Oedema		

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Peripheral swelling subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 127 (0.00%) 0	
Puncture site pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Secretion discharge subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Systemic inflammatory response syndrome subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 127 (0.00%) 0	
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Hypersensitivity subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 127 (0.00%) 0	
Multiple allergies subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Reproductive system and breast disorders Pelvic pain subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 127 (1.57%) 2	
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Breast pain subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 127 (0.00%) 0	
Erectile dysfunction			

subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Penile pain			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 35 (20.00%)	30 / 127 (23.62%)	
occurrences (all)	8	31	
Dyspnoea			
subjects affected / exposed	6 / 35 (17.14%)	22 / 127 (17.32%)	
occurrences (all)	6	26	
Nasal congestion			
subjects affected / exposed	3 / 35 (8.57%)	7 / 127 (5.51%)	
occurrences (all)	4	13	
Rhinorrhoea			
subjects affected / exposed	0 / 35 (0.00%)	5 / 127 (3.94%)	
occurrences (all)	0	6	
Dysphonia			
subjects affected / exposed	2 / 35 (5.71%)	2 / 127 (1.57%)	
occurrences (all)	2	2	
Dyspnoea exertional			
subjects affected / exposed	0 / 35 (0.00%)	4 / 127 (3.15%)	
occurrences (all)	0	4	
Hypoxia			
subjects affected / exposed	0 / 35 (0.00%)	4 / 127 (3.15%)	
occurrences (all)	0	4	
Oropharyngeal pain			
subjects affected / exposed	3 / 35 (8.57%)	1 / 127 (0.79%)	
occurrences (all)	3	1	
Pulmonary embolism			

subjects affected / exposed	0 / 35 (0.00%)	4 / 127 (3.15%)
occurrences (all)	0	4
Haemoptysis		
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)
occurrences (all)	1	2
Pleural effusion		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	3
Upper-airway cough syndrome		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	3
Wheezing		
subjects affected / exposed	3 / 35 (8.57%)	0 / 127 (0.00%)
occurrences (all)	3	0
Hiccups		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Laryngeal haemorrhage		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	2	1
Acute respiratory failure		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Bronchial secretion retention		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Epistaxis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Increased viscosity of upper respiratory secretion		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Laryngeal oedema		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0

Lung infiltration			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Orthopnoea			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pharyngeal erythema			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pleural fibrosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pleuritic pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pneumothorax			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Pulmonary hypertension			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Tachypnoea			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 35 (5.71%)	10 / 127 (7.87%)	
occurrences (all)	2	10	
Anxiety			

subjects affected / exposed	4 / 35 (11.43%)	7 / 127 (5.51%)	
occurrences (all)	4	7	
Depression			
subjects affected / exposed	3 / 35 (8.57%)	3 / 127 (2.36%)	
occurrences (all)	3	3	
Confusional state			
subjects affected / exposed	2 / 35 (5.71%)	3 / 127 (2.36%)	
occurrences (all)	3	3	
Restlessness			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Depressed mood			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Hallucination			
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Sleep disorder			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Agitation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Delirium			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Disorientation			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	2	
Investigations			
Weight decreased			
subjects affected / exposed	4 / 35 (11.43%)	22 / 127 (17.32%)	
occurrences (all)	4	28	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 35 (2.86%)	21 / 127 (16.54%)
occurrences (all)	1	21
Alanine aminotransferase increased		
subjects affected / exposed	1 / 35 (2.86%)	18 / 127 (14.17%)
occurrences (all)	1	19
Blood creatinine increased		
subjects affected / exposed	6 / 35 (17.14%)	9 / 127 (7.09%)
occurrences (all)	9	10
Lymphocyte count decreased		
subjects affected / exposed	0 / 35 (0.00%)	10 / 127 (7.87%)
occurrences (all)	0	10
Gamma-glutamyltransferase increased		
subjects affected / exposed	1 / 35 (2.86%)	7 / 127 (5.51%)
occurrences (all)	1	7
Amylase increased		
subjects affected / exposed	1 / 35 (2.86%)	6 / 127 (4.72%)
occurrences (all)	1	7
Blood alkaline phosphatase increased		
subjects affected / exposed	1 / 35 (2.86%)	4 / 127 (3.15%)
occurrences (all)	1	4
Blood creatine phosphokinase increased		
subjects affected / exposed	1 / 35 (2.86%)	4 / 127 (3.15%)
occurrences (all)	1	4
Eosinophil count increased		
subjects affected / exposed	0 / 35 (0.00%)	5 / 127 (3.94%)
occurrences (all)	0	5
Lipase increased		
subjects affected / exposed	2 / 35 (5.71%)	3 / 127 (2.36%)
occurrences (all)	2	4
Blood bilirubin increased		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	3
International normalised ratio increased		

subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)
occurrences (all)	1	2
Neutrophil count decreased		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	4
Platelet count decreased		
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)
occurrences (all)	1	3
Weight increased		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	4
Blood albumin decreased		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Blood lactate dehydrogenase increased		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Troponin I increased		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	1	1
Troponin increased		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
White blood cell count increased		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Blood calcium increased		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood creatine increased		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Blood creatine phosphokinase MB		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Blood folate decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Blood sodium decreased subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 2	0 / 127 (0.00%) 0	
Blood thyroid stimulating hormone decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Brain natriuretic peptide increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
C-reactive protein increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Clostridium test positive subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Electrocardiogram QT prolonged subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 127 (0.00%) 0	
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Neutrophil count increased			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 4	6 / 127 (4.72%) 7	
Hand fracture			
subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Infusion related reaction			
subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Procedural pain			
subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Thermal burn			
subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Vaccination complication			
subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Vascular access complication			
subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	5 / 127 (3.94%) 5	
Sinus tachycardia			
subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 127 (0.79%) 2	
Atrial fibrillation			

subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Pericardial effusion			
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Cardiac failure congestive			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 35 (28.57%)	10 / 127 (7.87%)	
occurrences (all)	11	11	
Headache			
subjects affected / exposed	6 / 35 (17.14%)	12 / 127 (9.45%)	
occurrences (all)	11	14	
Neuropathy peripheral			
subjects affected / exposed	2 / 35 (5.71%)	4 / 127 (3.15%)	
occurrences (all)	2	4	
Dysgeusia			
subjects affected / exposed	1 / 35 (2.86%)	4 / 127 (3.15%)	
occurrences (all)	1	4	
Paraesthesia			
subjects affected / exposed	1 / 35 (2.86%)	3 / 127 (2.36%)	
occurrences (all)	1	4	
Syncope			
subjects affected / exposed	0 / 35 (0.00%)	4 / 127 (3.15%)	
occurrences (all)	0	4	
Cognitive disorder			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Sinus headache			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences (all)	1	2	

Tremor		
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)
occurrences (all)	1	2
Ataxia		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Peripheral sensory neuropathy		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	2	1
Burning sensation		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Carotid artery stenosis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Carpal tunnel syndrome		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Disturbance in attention		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Dyskinesia		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Hyperaesthesia		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Hypersomnia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hypoaesthesia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hypotonia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Migraine			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Restless legs syndrome			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Somnolence			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vasogenic cerebral oedema			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Visual field defect			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 35 (8.57%)	20 / 127 (15.75%)	
occurrences (all)	3	31	
Eosinophilia			
subjects affected / exposed	2 / 35 (5.71%)	8 / 127 (6.30%)	
occurrences (all)	3	11	
Leukocytosis			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Neutropenia			
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)	
occurrences (all)	1	2	
Lymph node pain			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Lymphadenopathy			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Thrombocytopenia			

subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Anaemia of malignant disease			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Haemolytic anaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Leukopenia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Hearing impaired			
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)	
occurrences (all)	0	2	
Tinnitus			
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)	
occurrences (all)	1	1	
Deafness			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Deafness bilateral			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye swelling			

subjects affected / exposed	2 / 35 (5.71%)	2 / 127 (1.57%)
occurrences (all)	3	3
Vision blurred		
subjects affected / exposed	2 / 35 (5.71%)	2 / 127 (1.57%)
occurrences (all)	2	2
Dry eye		
subjects affected / exposed	2 / 35 (5.71%)	1 / 127 (0.79%)
occurrences (all)	2	1
Eyelid oedema		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	3
Periorbital oedema		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	2	2
Uveitis		
subjects affected / exposed	2 / 35 (5.71%)	0 / 127 (0.00%)
occurrences (all)	2	0
Blepharitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Erythema of eyelid		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Eye pain		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	2
Keratitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Lacrimation increased		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Meibomian gland dysfunction		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Metamorphopsia		

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Parophthalmia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vitreous floaters			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	14 / 35 (40.00%)	46 / 127 (36.22%)	
occurrences (all)	18	74	
Diarrhoea			
subjects affected / exposed	11 / 35 (31.43%)	35 / 127 (27.56%)	
occurrences (all)	24	46	
Vomiting			
subjects affected / exposed	11 / 35 (31.43%)	27 / 127 (21.26%)	
occurrences (all)	12	43	
Constipation			
subjects affected / exposed	3 / 35 (8.57%)	16 / 127 (12.60%)	
occurrences (all)	3	20	
Abdominal pain			
subjects affected / exposed	3 / 35 (8.57%)	7 / 127 (5.51%)	
occurrences (all)	4	7	
Dry mouth			
subjects affected / exposed	4 / 35 (11.43%)	6 / 127 (4.72%)	
occurrences (all)	4	6	
Dysphagia			
subjects affected / exposed	3 / 35 (8.57%)	6 / 127 (4.72%)	
occurrences (all)	3	6	

Stomatitis		
subjects affected / exposed	1 / 35 (2.86%)	7 / 127 (5.51%)
occurrences (all)	1	7
Dyspepsia		
subjects affected / exposed	2 / 35 (5.71%)	5 / 127 (3.94%)
occurrences (all)	2	5
Abdominal pain upper		
subjects affected / exposed	1 / 35 (2.86%)	4 / 127 (3.15%)
occurrences (all)	1	4
Gastrooesophageal reflux disease		
subjects affected / exposed	3 / 35 (8.57%)	1 / 127 (0.79%)
occurrences (all)	3	1
Colitis		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Flatulence		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	1	1
Gastritis		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Glossodynia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	1	1
Lip swelling		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	1	1
Toothache		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Abdominal discomfort		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Abdominal distension		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Abdominal hernia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Abdominal pain lower		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	3	0
Anal haemorrhage		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Aphthous ulcer		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Dental caries		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Gastric ulcer		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Gastrointestinal disorder		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Gingival pain		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Haemorrhoidal haemorrhage		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Mouth ulceration		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Oesophagitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Oral discomfort		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	5

Oral pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Rectal tenesmus			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Reflux gastritis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Hepatitis acute			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Liver disorder			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	8 / 35 (22.86%)	28 / 127 (22.05%)	
occurrences (all)	10	36	
Rash			
subjects affected / exposed	4 / 35 (11.43%)	24 / 127 (18.90%)	
occurrences (all)	4	26	
Rash maculo-papular			
subjects affected / exposed	5 / 35 (14.29%)	13 / 127 (10.24%)	
occurrences (all)	5	20	
Dry skin			

subjects affected / exposed	2 / 35 (5.71%)	13 / 127 (10.24%)
occurrences (all)	2	14
Urticaria		
subjects affected / exposed	0 / 35 (0.00%)	5 / 127 (3.94%)
occurrences (all)	0	8
Night sweats		
subjects affected / exposed	2 / 35 (5.71%)	2 / 127 (1.57%)
occurrences (all)	2	2
Alopecia		
subjects affected / exposed	1 / 35 (2.86%)	2 / 127 (1.57%)
occurrences (all)	1	2
Erythema		
subjects affected / exposed	2 / 35 (5.71%)	1 / 127 (0.79%)
occurrences (all)	2	3
Hyperhidrosis		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	3
Rash erythematous		
subjects affected / exposed	2 / 35 (5.71%)	1 / 127 (0.79%)
occurrences (all)	2	1
Skin lesion		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	3
Dermatitis		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Dermatitis acneiform		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Dermatitis allergic		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Palmar-plantar erythrodysesthesia syndrome		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2

Rash papular		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Rash pruritic		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	2	1
Skin exfoliation		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Blood blister		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Decubitus ulcer		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Dermatitis bullous		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Drug eruption		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hyperkeratosis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Keratolysis exfoliativa acquired		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Onycholysis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Prurigo		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Skin fissures		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Skin induration subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Skin ulcer subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Skin ulcer haemorrhage subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Swelling face subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Renal and urinary disorders			
Haematuria subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4	2 / 127 (1.57%) 2	
Proteinuria subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	2 / 127 (1.57%) 2	
Acute kidney injury subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 127 (1.57%) 2	
Dysuria subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 127 (1.57%) 2	
Pollakiuria subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 127 (0.79%) 2	
Anuria subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 127 (0.00%) 0	
Bladder discomfort subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Bladder spasm			

subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Chronic kidney disease			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Hydronephrosis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Leukocyturia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Micturition urgency			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Nocturia			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Oliguria			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Polyuria			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Urine odour abnormal			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	4 / 35 (11.43%)	15 / 127 (11.81%)	
occurrences (all)	4	16	

Hyperthyroidism subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	12 / 127 (9.45%) 12	
Adrenal insufficiency subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Androgen deficiency subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Thyroiditis acute subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 15	28 / 127 (22.05%) 30	
Back pain subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	13 / 127 (10.24%) 15	
Musculoskeletal pain subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 7	7 / 127 (5.51%) 7	
Myalgia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	6 / 127 (4.72%) 8	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	9 / 127 (7.09%) 10	
Muscular weakness subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	8 / 127 (6.30%) 9	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	5 / 127 (3.94%) 5	
Neck pain			

subjects affected / exposed	1 / 35 (2.86%)	4 / 127 (3.15%)
occurrences (all)	1	8
Flank pain		
subjects affected / exposed	3 / 35 (8.57%)	1 / 127 (0.79%)
occurrences (all)	3	1
Arthritis		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	3
Joint effusion		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	7
Joint swelling		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Muscle spasms		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	1	1
Bone pain		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Groin pain		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Joint instability		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Muscle contracture		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Musculoskeletal disorder		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Myalgia intercostal		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Myopathy		

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Osteoporosis			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Plantar fasciitis			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)	
occurrences (all)	1	0	
Tendon pain			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	5 / 35 (14.29%)	10 / 127 (7.87%)	
occurrences (all)	6	10	
Rash pustular			
subjects affected / exposed	1 / 35 (2.86%)	6 / 127 (4.72%)	
occurrences (all)	1	9	
Pneumonia			
subjects affected / exposed	0 / 35 (0.00%)	5 / 127 (3.94%)	
occurrences (all)	0	5	
Sinusitis			
subjects affected / exposed	2 / 35 (5.71%)	3 / 127 (2.36%)	
occurrences (all)	2	3	
Candida infection			
subjects affected / exposed	1 / 35 (2.86%)	3 / 127 (2.36%)	
occurrences (all)	1	4	
Influenza			
subjects affected / exposed	1 / 35 (2.86%)	3 / 127 (2.36%)	
occurrences (all)	1	5	
Lung infection			
subjects affected / exposed	0 / 35 (0.00%)	4 / 127 (3.15%)	
occurrences (all)	0	6	

Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	4 / 127 (3.15%) 4
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	2 / 127 (1.57%) 2
Corona virus infection subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	3 / 127 (2.36%) 3
Oral candidiasis subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 3	1 / 127 (0.79%) 2
Herpes zoster subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 127 (1.57%) 2
Pharyngitis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 127 (1.57%) 3
Rhinitis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 127 (1.57%) 2
Tooth infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 127 (0.79%) 1
Bronchitis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1
Clostridium difficile colitis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1
Clostridium difficile infection subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 127 (0.00%) 0
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 2

Cystitis		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	2	0
Device related infection		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Diverticulitis		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Gingivitis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Groin infection		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Hordeolum		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Mucosal infection		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Oesophageal candidiasis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Oropharyngeal candidiasis		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Otitis media		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Peripheral nerve infection		
subjects affected / exposed	1 / 35 (2.86%)	0 / 127 (0.00%)
occurrences (all)	1	0
Pneumonia klebsiella		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1

Pneumonia staphylococcal subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Sepsis subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Skin infection subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Vaginal infection subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	1 / 127 (0.79%) 1	
Metabolism and nutrition disorders			
Decreased appetite subjects affected / exposed occurrences (all)	13 / 35 (37.14%) 13	25 / 127 (19.69%) 29	
Hyponatraemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	16 / 127 (12.60%) 20	
Dehydration subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	12 / 127 (9.45%) 15	
Hypokalaemia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	12 / 127 (9.45%) 13	
Hypocalcaemia subjects affected / exposed occurrences (all)	6 / 35 (17.14%) 7	6 / 127 (4.72%) 7	
Hypomagnesaemia subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	6 / 127 (4.72%) 7	
Hypophosphataemia			

subjects affected / exposed	2 / 35 (5.71%)	4 / 127 (3.15%)
occurrences (all)	2	4
Hypercalcaemia		
subjects affected / exposed	1 / 35 (2.86%)	4 / 127 (3.15%)
occurrences (all)	1	5
Hyperglycaemia		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	6
Hyperkalaemia		
subjects affected / exposed	0 / 35 (0.00%)	3 / 127 (2.36%)
occurrences (all)	0	3
Hyperuricaemia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	1	1
Hypoalbuminaemia		
subjects affected / exposed	0 / 35 (0.00%)	2 / 127 (1.57%)
occurrences (all)	0	2
Hypovolaemia		
subjects affected / exposed	1 / 35 (2.86%)	1 / 127 (0.79%)
occurrences (all)	1	1
Cachexia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Folate deficiency		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hypertriglyceridaemia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hypervolaemia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Hypoglycaemia		
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)
occurrences (all)	0	1
Insulin resistance		

subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Malnutrition			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	
Vitamin D deficiency			
subjects affected / exposed	0 / 35 (0.00%)	1 / 127 (0.79%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2017	<p>Modified timing of safety observations in Cycle 1 to include additional monitoring during Days 1-3 and to remove monitoring on Days 6-11 to reduce the number of overall assessments and study visits; removed clinical site visits for physical examinations and ECGs for Days 4, 5, and 11 of Cycles 1 and 2.</p> <p>Added IV fluid administration on Days 1 and 2 of Cycle 1.</p> <p>Updated timing of the End of Treatment visit based on which study drug(s) the patient was receiving.</p> <p>Reduced the frequency of PK sampling in Cycle 2 from Days 1-5, 8, and 11 to Days 1 and 8 only.</p> <p>Updated inclusion criterion 8h to include an upper limit on lipase and amylase levels to $< 3 \times \text{ULN}$ (if there were neither clinical nor radiographic signs of pancreatitis).</p> <p>Modified the eligibility criteria to exclude patients who have a diagnosis of NSCLC and require supplemental oxygen.</p> <p>Modified the eligibility criteria to exclude patients in whom checkpoint inhibitor therapy was intolerable and required discontinuation of treatment.</p> <p>Modified and clarified the language for long-term follow up to evaluate tumor data and/or scans for patients who started a new anti-cancer therapy.</p> <p>Added a requirement that patients be re-consented if the treating physician recommends continuing treatment following disease progression.</p> <p>Added "any Grade 4 nausea or vomiting" to DLT list.</p> <p>Modified criteria for Grade 3 or 4 AEs that should not be considered a DLT</p> <p>Removed information on Grade 4 toxicities for NKTR-214 dose delay and reduction criteria</p> <p>Added information on Grade 4 amylase or lipase to the permanent treatment discontinuation criteria</p> <p>Added language "suspected" or "known" disease progression for tumor biopsies.</p> <p>Added section on IMAE reporting.</p> <p>Removed section on response criteria using irRECIST.</p> <p>Updated language in section on Changes to the Protocol to allow an administrative letter describing protocol changes to be used by the Sponsor.</p> <p>Updated section on language on quality control and quality assurance</p>

21 September 2017	<p>Added select on-label indications for pembrolizumab (locally advanced or metastatic melanoma, locally advanced or metastatic urothelial bladder cancer, or metastatic NSCLC) as a second combination treatment option; title updated to reflect the addition of pembrolizumab.</p> <p>Added disease-specific inclusion criteria.</p> <p>Changed planned number of study sites, anticipated enrollment, and duration for infusion of NKTR-214 from 15 (\pm5) min to 30 (\pm5) min.</p> <p>Updated protocol introduction to include safety information about clinical experience with NKTR-214, and to remove nonclinical data.</p> <p>Changed inclusion criterion for demonstration of adequate organ function to within 28 days of treatment initiation and descriptions of eligibility criteria regarding duration of post-study contraception use and duration of follow up for pregnancy from 3 mos to 5.</p> <p>Modified enrollment into cohorts to clarify that each cohort may enroll any combination of patients with any of the eligible tumor types; modified to clarify that the first 3 patients in each cohort were to be dosed to allow evaluation of DLTs and that the cohort may then be immediately expanded to 6 patients if no DLT occurred in the first 3 patients.</p> <p>Changed timing for predose blood sample collection for clinical lab tests.</p> <p>Updated postdose monitoring, intensive vital sign measurements, and hydration guidelines</p> <p>Revised EOT visit, and follow-up visit time windows.</p> <p>Modified reasons for EOT.</p> <p>Clarified timing of PK assessments.</p> <p>Updated recommendations regarding treatment of infusion reactions to include NKTR-214 and pembrolizumab.</p> <p>Updated the list of AEs that should not be considered a DLT.</p> <p>Removed 24-hr reporting requirement for Gr 3 or higher imAEs.</p> <p>Specified that ECGs should be conducted predose.</p> <p>Updated timing for confirmation radiologic exam.</p> <p>Removed the requirement for HLA typing at screening.</p> <p>Removed exp. obj. to evaluate preliminary efficacy of NKTR-214 in combo with pembro and atezo</p>
21 November 2017	<p>Simplified study title.</p> <p>Lowered the minimum requirement for GFR in inclusion criterion 8e from ≥ 40 to ≥ 15 mL/min for patients with urothelial carcinoma who were cisplatin-ineligible.</p> <p>Clarified inclusion criterion 18b about known EGFR or ALK mutations applies only to non-squamous NSCLC.</p> <p>Replaced stress ECHO at baseline and at EOT with a standard ECHO; added language to allow for stress ECHO in the event of an abnormal standard ECHO, per clinical judgement; added language allowing for the flexibility to eliminate the need for a standard ECHO if deemed unnecessary by the Safety Review Committee.</p> <p>Capped continuation of treatment in patients with a confirmed complete response at a maximum of 2 years.</p> <p>Edited language about the end of treatment visit to clarify timing</p> <p>Corrected inconsistent language in the radiographic tumor assessment section and long-term follow-up section.</p> <p>Changed timing for the required on-treatment tumor biopsy from Days 15-25 to Days 15-21 after the first dose.</p> <p>Changed duration of stable disease from ≥ 84 days (12 weeks) to ≥ 7 weeks for the definition clinical benefit rate.</p> <p>Added collection of bi-dimensional measurements from sites.</p> <p>Added language allowing prophylaxis for flu-like symptoms and/or rash/pruritus</p>
29 May 2018	<p>Removed dose escalation cohorts; NKTR-214 dose was established at 0.006 mg/kg given IV q3w.</p> <p>Removed description of DLT.</p> <p>Modified tumor types and treatments to be studied in each tumor type.</p> <p>Updated of inclusion/exclusion criteria.</p> <p>Aligned with PIVOT-02 Amendment 6.0.</p>

20 August 2019	<p>Updated figure of study schematic and schedule of assessments tables.</p> <p>Added the INN for NKTR-214 to the protocol.</p> <p>Updated clinical experience with NKTR-214.</p> <p>Added dose optimization cohorts and dose expansion cohort and rationale for their addition to the protocol.</p> <p>Added description of DLT.</p> <p>Modified of the tumor types and treatments to be studied in each tumor type.</p> <p>Updated inclusion/exclusion criteria</p> <p>Aligned with PIVOT-02 Amendment 6.0</p>
11 September 2019	First version of protocol submitted to Germany
06 December 2019	Removed possibility of collecting survival data beyond the end of study period
10 January 2020	<p>Exclusion of patients with PD-L1 < 50% from first-line NSCLC dose expansion cohorts</p> <p>Addition of ROS1 among tumor aberrations excluded in first line NSCLC dose expansion population cohorts</p> <p>Changed inclusion limit for patients from systolic < 150 mm Hg to < 140 mm Hg</p> <p>Added requirement of social security coverage</p> <p>Added exclusions of patients who received a live vaccine within 30 days of first study dose and patients with known history of active tuberculosis</p>
10 February 2020	<p>Updated the NKTR-214 clinical experience to include a summary of the CVA events observed in 16-214-02</p> <p>Implemented add'l safety measures to mitigate the risk of CVA events</p> <p>Added plasma samples for exploratory biomarker analyses for CVA characterization</p> <p>Modified instructions for NKTR-214 dose delay/reduction and criteria to resume study drug</p> <p>Added the re-trtmt criteria for renal fx and permanent trtmt discon in the CVA AE mngmt algorithm, the local lab tests prior to study drug, and a new appx to clarify definitions and methods of contraception for women of childbearing potential</p> <p>Updated inclusion criteria in both the dose optimization and dose exp cohorts such that pts must not have progressed within 6 mos of receiving radiation, surgery, adj, neoadj, or systemic therapy for cancer trtmt</p> <p>Clarified the definition of a line of prior therapy</p> <p>Excluded pts with c-ros oncogene and BRAF v600e for the dose exp phase</p> <p>Changed the exclusion for cardiovascular hx from the previous 2 yrs to 12 mos</p> <p>Excluded pts in subgroup PD-L1 < 1-49%, updated screening blood pressure to systolic < 140 mm Hg, added requirement that enrolled pts be affiliated to a Social Security System; and excluded pts who received a live vaccine within 30d prior to first dose and those with a known history of active tuberculosis (France only)</p> <p>Added that pelvic radiographic assessment is NA (Germany only)</p> <p>Updated NKTR-214 MOA, SOE, hydration guidelines, SAE reporting rqmts to indicate that AEs of special interest followed the same timeline as SAE reporting, and the recommendation for the contraception timeperiod for men following the last dose to 4 mos</p> <p>Removed possibility of collecting survival data beyond the end of study</p> <p>Added a section on the effect of NKTR-214 on conmed metabolism and the CVA AE mngmt algorithm, an appx on CVA mngmt algorithm, and sections on imAEs and potential DILI and section on AEs of special interest to cover CVA events</p> <p>Divided Appx 1 displaying lab tests</p>
01 November 2020	Added specific guidance in the event of cytokine release syndrome occurrence

23 December 2020	<p>Added Cohort 3 as contingency plan if Cohort 2 fails; 58 response evaluable first-line NSCLC patients could be enrolled in Cohort 3.</p> <p>Added cohorts of a chemotherapy combination to support Phase 3 with NKTR-214/pembrolizumab chemotherapy combination: Cohort 4 (non-squamous) and Cohort 5 (squamous).</p> <p>Added CRS appendix.</p> <p>Updated with newest version of CTCAE (per CTCAE v5.0).</p> <p>Updated the language regarding minimum duration on study for stable disease.</p> <p>Updated text on regarding flushing of the IV line after NKTR-214 infusion</p> <p>Updated with administrative clarifications and edits</p>
27 April 2021	<p>Added early stopping and safety monitoring rules for dose expansion Cohorts 4 and 5.</p> <p>Added DLTs to be evaluated in expansion phases.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was terminated early due to closure of the NKTR-214 clinical program.

Notes: