Clinical trial results:
An open-label Phase Ib/ II, multi-center study of 4SC-202 in Combination with Pembrolizumab in Patients with Unresectable Stage III/Metastatic Stage IV Cutaneous Melanoma primary refractory/non-responding to prior Anti-PD-1 Therapy – The SENSITIZE Study

Summary

EudraCT number	2017-001050-33
Trial protocol	DE IT
Global end of trial date	02 February 2022

Results information

Result version number	v1 (current)
This version publication date	15 February 2023
First version publication date	15 February 2023

Trial information

Trial identification

Sponsor protocol code	4SC-202-2-2017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03278665
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	4SC AG
Sponsor organisation address	Fraunhoferstr. 22, Planegg-Martinsried, Germany, 82152
Public contact	Corporate Communications, 4SC AG, 4SC AG, 0049 897007630, public@4sc.com
Scientific contact	Clinical Development, 4SC AG, 4SC AG, 0049 897007630, medical.request@4sc.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	29 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2021
Global end of trial reached?	Yes
Global end of trial date	02 February 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine safety and tolerability of combination treatment with domatinostat and Pembrolizumab in patients with advanced cutaneous malignant melanoma who are primary refractory or non-responding to anti-PD-1 mono or combination therapy.

Protection of trial subjects:

The dose escalation phase (Phase Ib) followed a modified "rolling six" design. Cohorts of patients received pre-defined escalating doses of domatinostat in combination with Pembrolizumab. Dose escalation decisions were made by the Safety Review Committee (SRC), considering the safety and tolerability data from the dose limiting toxicity (DLT) period. If 1 of 3 subjects experienced a DLT, the dose level was expanded to at least 6 patients. If the next higher dose level had already been opened after clearance of the first 3 subjects, further enrollment in this next higher dose level was interrupted. The SRC decided depending on the type and nature of the DLT(s) if a dose reduction in ongoing subjects of this next higher dose level was mandatory. If a dose level was considered non-tolerable, the previous dose level was expanded to 6 subjects to determine the MTD. If 2 or more subjects experienced DLTs in a dose levels, enrollment was interrupted and the SRC was convened for an ad-hoc meeting to decide on the further procedures.
Toxicity management guidelines were given in the protocol requiring interruption, reduction or discontinuation of domatinostat treatment, depending on the severity of the toxicity. Before the start of a new treatment cycle subjects were assessed including AEs, physical examination, and measurement of hematological and biochemical parameters. Depending on the observed toxicities, treatment was to be interrupted and could only be re-started after the toxicity had resolved. For any events that fulfilled DLT criteria, the dose of domatinostat had to be reduced at re-start. Reduced doses could not be increased for the remainder of the trial. Subjects requiring more than 2 dose reductions had to be discontinued.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	27
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study participants were enrolled from 9-Nov-2017 to 19-Nov-2020 at 6 centers in Germany and 1 in Italy.

Pre-assignment

Screening details:

51 subjects were screened, of which 11 subjects were screening failures due to not meeting inclusion criteria (3 subjects) or meeting exclusion criteria (8 subjects).

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	100 mg once daily 14+7 (DL1)

Arm description:

100 mg domatinostat once daily treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.

Arm type	Experimental
Investigational medicinal product name	Domatinostat
Investigational medicinal product code	4SC-202
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A once daily oral dose of domatinostat (1 x 100 mg tablet) was taken within 2 hours after a light breakfast in the morning. On study days 1, 2, 14 and 15 of the first cycle and Day 1 of the second cycle the tables were taken after blood samples for PK analysis were drawn and more than 2 hours after having a light breakfast. The tablets were not to be chewed and/or crushed and were swallowed together with about 200 ml of noncarbonated water (e.g. tap water) at room temperature.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg Pembrolizumab i.v. once every 3 weeks, administered prior to domatinostat dosing.

Arm title	200 mg once daily 14+7 (DL2a)

Arm description:

200 mg domatinostat once daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.

Arm type	Experimental
Investigational medicinal product name	Domatinostat
Investigational medicinal product code	4SC-202
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A once daily oral dose of domatinostat (2 x 100 mg tablet) was taken after a fasting period of at least 2 hours. On study days 1, 2, 14 and 15 of the first cycle and Day 1 of the second cycle the tables were taken after blood samples for PK analysis were drawn and after a fasting period of at least 2 hours. The tablets were not to be chewed and/or crushed and were swallowed together with about 200 ml of noncarbonated water (e.g. tap water) at room temperature.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg Pembrolizumab i.v. once every 3 weeks, administered prior to domatinostat dosing.

Arm title	200 mg twice daily 14+7 (DL3)

Arm description:

200 mg domatinostat twice daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.

Arm type	Experimental
Investigational medicinal product name	Domatinostat
Investigational medicinal product code	4SC-202
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A twice daily oral dose of domatinostat (2 x 100 mg tablet twice daily) was taken after a fasting period of at least 2 hours. On study days 1, 2, 14 and 15 of the first cycle and Day 1 of the second cycle the tables were taken after blood samples for PK analysis were drawn and after a fasting period of at least 2 hours. The tablets were not to be chewed and/or crushed and were swallowed together with about 200 ml of noncarbonated water (e.g. tap water) at room temperature.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg Pembrolizumab i.v. once every 3 weeks, administered prior to domatinostat dosing.

Arm title	200 mg once daily 21 days (DL2b)

Arm description:

200 mg domatinostat once daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.

Arm type	Experimental
Investigational medicinal product name	Domatinostat
Investigational medicinal product code	4SC-202
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A once daily oral dose of domatinostat (2 x 100 mg tablet) was taken after a fasting period of at least 2 hours. On study days 1, 2, 14 and 15 of the first cycle and Day 1 of the second cycle the tables were taken after blood samples for PK analysis were drawn and after a fasting period of at least 2 hours. The tablets were not to be chewed and/or crushed and were swallowed together with about 200 ml of noncarbonated water (e.g. tap water) at room temperature.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion, Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg Pembrolizumab i.v. once every 3 weeks, administered prior to domatinostat dosing.

Arm title	200 mg twice daily 21 days (DL4)

Arm description:

200 mg domatinostat twice daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.

Arm type	Experimental
Investigational medicinal product name	Domatinostat
Investigational medicinal product code	4SC-202
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

A twice daily oral dose of domatinostat (2 x 100 mg tablet twice daily) was taken after a fasting period of at least 2 hours. On study days 1, 2, 14 and 15 of the first cycle and Day 1 of the second cycle the tables were taken after blood samples for PK analysis were drawn and after a fasting period of at least 2 hours. The tablets were not to be chewed and/or crushed and were swallowed together with about 200 ml of noncarbonated water (e.g. tap water) at room temperature.

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion, Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 mg/kg Pembrolizumab i.v. once every 3 weeks, administered prior to domatinostat dosing.

Number of subjects in period 1	100 mg once daily 14+7 (DL1)	200 mg once daily 14+7 (DL2a)	200 mg twice daily 14+7 (DL3)
Started	10	6	7
Completed	10	6	7

Number of subjects in period 1	200 mg once daily 21 days (DL2b)	200 mg twice daily 21 days (DL4)
Started	7	10
Completed	7	10

Baseline characteristics

Reporting groups	
Reporting group title	100 mg once daily 14+7 (DL1)
Reporting group description:	
100 mg domatinostat once daily treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.	
Reporting group title	200 mg once daily 14+7 (DL2a)
Reporting group description:	
200 mg domatinostat once daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.	
Reporting group title	200 mg twice daily 14+7 (DL3)
Reporting group description:	
200 mg domatinostat twice daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.	
Reporting group title	200 mg once daily 21 days (DL2b)
Reporting group description:	
200 mg domatinostat once daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.	
Reporting group title	200 mg twice daily 21 days (DL4)
Reporting group description:	
200 mg domatinostat twice daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.	

Reporting group values	100 mg once daily 14+7 (DL1)	200 mg once daily 14+7 (DL2a)	200 mg twice daily 14+7 (DL3)
Number of subjects	10	6	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	4	5
From 65-84 years	3	2	2
85 years and over	0	0	0
Age continuous Units: years			
median	59.0	55.0	55.0
full range (min-max)	23 to 79	30 to 80	29 to 76
Gender categorical Units: Subjects			
Female	4	3	1
Male	6	3	6

Reporting group values	200 mg once daily 21 days (DL2b)	200 mg twice daily 21 days (DL4)	Total
Number of subjects	7	10	40

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3	8	27
From 65-84 years	4	2	13
85 years and over	0	0	0
Age continuous Units: years			
median	69.0	59.5	
full range (min-max)	46 to 79	46 to 78	-
Gender categorical Units: Subjects			
Female	2	4	14
Male	5	6	26

End points

End points reporting groups

Reporting group title	100 mg once daily 14+7 (DL1)
Reporting group description:	
100 mg domatinostat once daily treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.	
Reporting group title	200 mg once daily 14+7 (DL2a)
Reporting group description:	
200 mg domatinostat once daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.	
Reporting group title	200 mg twice daily 14+7 (DL3)
Reporting group description:	
200 mg domatinostat twice daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.	
Reporting group title	200 mg once daily 21 days (DL2b)
Reporting group description:	
200 mg domatinostat once daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.	
Reporting group title	200 mg twice daily 21 days (DL4)
Reporting group description:	
200 mg domatinostat twice daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.	

Primary: Number of subjects with treatment-emergent adverse events

End point title	Number of subjects with treatment-emergent adverse events[1]
End point description:	
Safety and tolerability of the combination of 4SC-202 and Pembrolizumab will be assessed from adverse events, laboratory tests, vital signs, ECGs, ECOG PS, physical examination and assessment of concomitant medications.	
End point type	Primary
End point timeframe:	
From treatment start until 20 weeks (±2 weeks) after the last dose of domatinostat or Pembrolizumab, whichever was later.	
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: Only descriptive analysis was done: Continuous variables were summarized using descriptive statistics by reporting the number of non-missing observations, arithmetic mean, standard deviation, median, minimum and maximum. Categorical variables were summarized using frequency tables showing the number and percentage of patients within a particular category.	

End point values	100 mg once daily 14+7 (DL1)	200 mg once daily 14+7 (DL2a)	200 mg twice daily 14+7 (DL3)	200 mg once daily 21 days (DL2b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	6	7	7
Units: subjects	10	6	7	7

End point values	200 mg twice			

	daily 21 days (DL4)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: subjects	10			

Statistical analyses

No statistical analyses for this end point

Primary: Number of treatment-emergent adverse events

End point title	Number of treatment-emergent adverse events[2]

End point description:

Safety and tolerability of the combination of 4SC-202 and Pembrolizumab will be assessed from adverse events, laboratory tests, vital signs, ECGs, ECOG PS, physical examination and assessment of concomitant medications.

End point type	Primary

End point timeframe:

From treatment start until 20 weeks (±2 weeks) after the last dose of domatinostat or Pembrolizumab, whichever was later.

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: Only descriptive analysis was done: Continuous variables were summarized using descriptive statistics by reporting the number of non-missing observations, arithmetic mean, standard deviation, median, minimum and maximum. Categorical variables were summarized using frequency tables showing the number and percentage of patients within a particular category.

End point values	100 mg once daily 14+7 (DL1)	200 mg once daily 14+7 (DL2a)	200 mg twice daily 14+7 (DL3)	200 mg once daily 21 days (DL2b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	6	7	7
Units: adverse events	109	93	173	103

End point values	200 mg twice daily 21 days (DL4)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: adverse events	177			

Statistical analyses

No statistical analyses for this end point

Primary: Number of patients with Dose limiting toxicities (DLTs)

End point title	Number of patients with Dose limiting toxicities (DLTs)[3]

End point description:

Safety and tolerability of the combination of 4SC-202 and Pembrolizumab will be assessed from adverse events, laboratory tests, vital signs, ECGs, ECOG PS, physical examination and assessment of concomitant medications.

End point type	Primary

End point timeframe:

From treatment start to the end of the second cycle with combination therapy (i.e, in the dosing schedules with 7 days off dose, Cycle 1 to Cycle 3; in continuous dosing schedules, Cycle 1 to Cycle 2)

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: Only descriptive analysis was done: Continuous variables were summarized using descriptive statistics by reporting the number of non-missing observations, arithmetic mean, standard deviation, median, minimum and maximum. Categorical variables were summarized using frequency tables showing the number and percentage of patients within a particular category.

End point values	100 mg once daily 14+7 (DL1)	200 mg once daily 14+7 (DL2a)	200 mg twice daily 14+7 (DL3)	200 mg once daily 21 days (DL2b)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	6	7	7
Units: subjects	1	1	1	1

End point values	200 mg twice daily 21 days (DL4)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for collection of AEs extended from ICF signature until 20 weeks (±2 weeks) after the last dose of domatinostat or Pembrolizumab, whichever was later.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	100 mg once daily 14+7 (DL1)

Reporting group description:

100 mg domatinostat once daily treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.

Reporting group title	200 mg once daily 14+7 (DL2a)

Reporting group description:

200 mg domatinostat once daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.

Reporting group title	200 mg twice daily 14+7 (DL3)

Reporting group description:

200 mg domatinostat twice daily, treatment for 14 consecutive days followed by 7 days off treatment, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 2 Day 1 onwards.

Reporting group title	200 mg once daily 21 days (DL2b)

Reporting group description:

200 mg domatinostat once daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.

Reporting group title	200 mg twice daily 21 days (DL4)

Reporting group description:

200 mg domatinostat twice daily treatment for 21 consecutive days, and 2 mg/kg Pembrolizumab i.v. once every 3 weeks from Cycle 1 Day 1 onwards.

Serious adverse events	100 mg once daily 14+7 (DL1)	200 mg once daily 14+7 (DL2a)	200 mg twice daily 14+7 (DL3)
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	4 / 6 (66.67%)	5 / 7 (71.43%)
number of deaths (all causes)	4	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Tumour haemorrhage			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Tumour pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Embolism			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (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
Inferior vena caval occlusion			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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 compression			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Surgical and medical procedures			
Endodontic procedure			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (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
General disorders and administration			

site conditions			
General physical health deterioration			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related thrombosis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Pyrexia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Respiratory, thoracic and mediastinal disorders			
immune-mediated pneumonitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Nasal polyps			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Pneumothorax			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Extrasystoles			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	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
Ventricular extrasystoles			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune colitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Chronic gastritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Colitis			

subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Ileus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (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
Subileus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Endocrine disorders			
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis			

subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	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
Neutropenic infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (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
Pharyngitis bacterial			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	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
Skin infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	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
Tonsillitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (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

Serious adverse events	200 mg once daily 21 days (DL2b)	200 mg twice daily 21 days (DL4)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 7 (71.43%)	8 / 10 (80.00%)	
number of deaths (all causes)	1	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inferior vena caval occlusion			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular compression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Endodontic procedure			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related thrombosis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug hypersensitivity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
immune-mediated pneumonitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Intracranial pressure increased			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autoimmune colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Lymphocytic hypophysitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	100 mg once daily 14+7 (DL1)	200 mg once daily 14+7 (DL2a)	200 mg twice daily 14+7 (DL3)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	6 / 6 (100.00%)	7 / 7 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lymph nodes			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0

Vascular disorders			
Embolism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	3
Lymphoedema			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	2	1	1
Hypertension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	4 / 7 (57.14%)
occurrences (all)	3	1	8
Pain			
subjects affected / exposed	2 / 10 (20.00%)	4 / 6 (66.67%)	2 / 7 (28.57%)
occurrences (all)	2	5	3
Pyrexia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	1 / 7 (14.29%)
occurrences (all)	3	7	1
General physical health deterioration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	2	2	2
Chills			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	0	3	2
Localised oedema			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Dyspnoea			
subjects affected / exposed	2 / 10 (20.00%)	2 / 6 (33.33%)	4 / 7 (57.14%)
occurrences (all)	2	3	4
Cough			
subjects affected / exposed	1 / 10 (10.00%)	3 / 6 (50.00%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Pleural effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pulmonary haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Alanine aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	0 / 7 (0.00%)
occurrences (all)	0	3	0
Lipase increased			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	2
Blood bilirubin increased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Glomerular filtration rate decreased0			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Platelet count decreased			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Wound complication			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			

Sinus tachycardia			
subjects affected / exposed	2 / 10 (20.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Dizziness			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Dysgeusia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	1	1	33
Thrombocytopenia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Tinnitus			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	3 / 10 (30.00%)	1 / 6 (16.67%)	4 / 7 (57.14%)
occurrences (all)	7	2	4
Diarrhoea			
subjects affected / exposed	5 / 10 (50.00%)	2 / 6 (33.33%)	3 / 7 (42.86%)
occurrences (all)	7	2	6

Nausea			
subjects affected / exposed	4 / 10 (40.00%)	0 / 6 (0.00%)	3 / 7 (42.86%)
occurrences (all)	5	0	3
Abdominal pain			
subjects affected / exposed	2 / 10 (20.00%)	1 / 6 (16.67%)	2 / 7 (28.57%)
occurrences (all)	2	1	2
Colitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	3
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	1	1	1
Dry mouth			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	2 / 6 (33.33%)	1 / 7 (14.29%)
occurrences (all)	1	2	1
Eczema			

subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Xeroderma			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Drug eruption			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Erythema multiforme			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Intertrigo			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Rash			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urticaria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vitiligo			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	3
Hyperthyroidism			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Back pain			

subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Muscle spasms			
subjects affected / exposed	0 / 10 (0.00%)	0 / 6 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Flank pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Myalgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	1 / 7 (14.29%)
occurrences (all)	0	2	1
Nasopharyngitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 6 (16.67%)	1 / 7 (14.29%)
occurrences (all)	3	1	3
Rhinitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)	2 / 6 (33.33%)	2 / 7 (28.57%)
occurrences (all)	0	2	2
Hyponatraemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 6 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1

Non-serious adverse events	200 mg once daily 21 days (DL2b)	200 mg twice daily 21 days (DL4)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	10 / 10 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Metastases to lymph nodes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Lymphoedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 7 (14.29%)	5 / 10 (50.00%)	
occurrences (all)	1	8	
Pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
General physical health deterioration			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Chills			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Localised oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Non-cardiac chest pain			

subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Cough			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	1 / 7 (14.29%)	4 / 10 (40.00%)	
occurrences (all)	3	7	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 7 (28.57%)	2 / 10 (20.00%)	
occurrences (all)	2	3	
C-reactive protein increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	3 / 10 (30.00%)	
occurrences (all)	0	3	
Blood creatine phosphokinase increased			

subjects affected / exposed	2 / 7 (28.57%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Lipase increased			
subjects affected / exposed	2 / 7 (28.57%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 7 (14.29%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	3	
Weight decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
White blood cell count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
Blood bilirubin increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Glomerular filtration rate decreased0			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	5	1	
Injury, poisoning and procedural complications			

Wound complication			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 7 (14.29%)	2 / 10 (20.00%)	
occurrences (all)	1	3	
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dysgeusia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Paraesthesia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	4 / 7 (57.14%)	6 / 10 (60.00%)	
occurrences (all)	4	6	
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	4 / 10 (40.00%)	
occurrences (all)	1	10	
Nausea			
subjects affected / exposed	2 / 7 (28.57%)	6 / 10 (60.00%)	
occurrences (all)	2	10	
Abdominal pain			
subjects affected / exposed	1 / 7 (14.29%)	3 / 10 (30.00%)	
occurrences (all)	1	4	
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Gastritis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Stomatitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	2 / 7 (28.57%)	2 / 10 (20.00%)	
occurrences (all)	2	5	

Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Xeroderma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Drug eruption			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Erythema multiforme			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Intertrigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Urticaria			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Vitiligo			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Hyperthyroidism			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Back pain			
subjects affected / exposed	1 / 7 (14.29%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Muscular weakness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Myalgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 10 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 7 (14.29%)	4 / 10 (40.00%)	
occurrences (all)	1	5	
Hyponatraemia			
subjects affected / exposed	2 / 7 (28.57%)	1 / 10 (10.00%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2017	The changes introduced by this amendment were performed to modify the required contraceptive measures and pregnancy testing, increase the duration of SAE and AE monitoring to a minimum of 18 weeks after last study drug administration, clarify the dose of domatinostat in Cycle 1, and correct minor typos and inconsistencies.
06 June 2018	The changes introduced by this amendment were performed to modify the in- and exclusion criteria (i.e. clarify allowed prior anti-PD-1 antibody or combination therapies; consent of FCBP to comply with contraceptive requirement), remove the requirement of an anti-PD-1 monotherapy (provided that a 4-week wash-out period for anti-CTLA-4 antibody was performed upon receipt of prior combination therapy), add guidance on expected immune-mediated adverse reactions for pembrolizumab, allow simultaneous recruitment into the next dose level after clearance of the first 3 patients in a dose level, administer domatinostat in fasted state (to minimize variability in PK analyses), introduce a new dosing schedule in case of non-tolerability (3-day on/ 4-day off regime), add precautions for concomitant administration of domatinostat and strong inhibitors or inducers of CYP3A4 (based on in vitro findings) and of domatinostat and proton-pump-inhibitors (based on pH-dependency of domatinostat resorption), and to correct minor typos and inconsistencies as well as readability.
09 August 2018	National Amendment for USA only, provided in response to advice from the FDA. The changes introduced by this amendment were performed to define or explain more precisely the prior exposure to anti-PD-1 therapy, the recovery from non-hematological toxicities related to domatinostat (resolved to Grade 1 before re-start of study treatment), and the use of pembrolizumab at US study sites (commercial product to be sourced in US); furthermore, to add a clarification that toxicity associated with immunotherapy will be considered for determination of the MTD, specify the irRECIST criteria, add information on FDA approvals of PD-1 inhibitors, align the protocol toxicity guidelines with the SmPC of Keytruda, to revise the calculation of AE duration, and remove inconsistencies between synopsis and main text of the protocol.
07 May 2019	The changes introduced by this amendment were performed to introduce a continuous dosing schedule for domatinostat (including an optional participation in taking sequential tumor biopsies), allow more than one expansion cohort (to be specified in a separate Amendment, if applicable), remove the optional DL "-1" (not required since the first dose level was tolerated), allow intra-patient dose escalation after the first tumor assessment following Cycle 4 into the next higher dose level (provided this dose level has been declared as tolerable by the SRC), remove asymptomatic increases of amylase and/or lipase from the list of DLTs (provided AEs resolved by ≥ 1 grade within 7 days of treatment interruption), and align the protocol toxicity guidelines with the SmPC of Keytruda. In addition, minor issues were clarified and inconsistencies between synopsis and main text of the protocol were removed.
18 June 2019	The changes introduced by this amendment were performed to inform about the availability of the additional vial strength of 100 mg concentrate of pembrolizumab (in addition to 50 mg concentrate of pembrolizumab) and to correct minor inconsistencies and typos of the protocol.

13 January 2020	The changes introduced by this amendment were performed to change the dose in DL 4 (from 300 mg TDD into 400 mg TDD in a continuous dose schedule), introduce the collection of blood samples for a 24 h PK profile in DL 4 after administration of a single dose of 400 mg domatinostat, remove the restriction to formulation II in cohorts with continuous dosing schedule (i.e. formulation I also might have been applied), re-introduce a mandatory biopsy at screening and in Cycle 1, align the criteria for start of a new treatment cycle in continuous dosing with the criteria for start of treatment after an interruption, remove too detailed information on statistics, extend the time window for weight to determine the pembrolizumab dose (up to 3 days prior to first treatment), restrict the reporting of immediately reportable events (IRE) to the DLT period, add precautions regarding use of substrates of the CYP enzymes 2C8 or 2C9 and the transporters BCRP and OATP1B1, and correct typos of the protocol.
10 March 2020	The changes introduced by this amendment were performed to modify the protocol toxicity guidelines for handling of rash and allergic/hypersensitivity reactions (including optional skin biopsies in case of skin reactions).
09 September 2020	The changes introduced by this amendment were performed to modify the duration of treatment (discontinuation of treatment with pembrolizumab at the earliest one year after the first documentation of at least irSD), remove the option for domatinostat monotherapy in individual patients after the end of study (no regulatory-compliant procedure available), clarify the requirement of biopsies for the different dose levels, the intra-individual dose escalation (switch between schedules not allowed), melanoma staging for inclusion and body weight to be used for determination of pembrolizumab dose, remove inconsistencies in definitions of "best overall response" and "disease control rate", total sample size estimate and PK sampling (regarding 10 h and 12 h PK samples), and align the protocol toxicity guidelines of pembrolizumab with the updated recommendations in the SmPC.
22 October 2021	The changes introduced by this amendment were performed to limit the follow-up for survival to 52 weeks after the first dose of trial medication. Patients who remained on treatment for more than 52 weeks (up to the maximum of 102 weeks), were to be followed up for survival up to 20 weeks after the last study drug administration.

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.

Due to the limited number of patients treated in this trial, no conclusion can be drawn regarding a potential effect of domatinostat on the frequency of immune-related events.
Survival data was incomplete with 17 of the 40 patients being censored.

Notes: