Clinical trial results:
Open-Label, Multi-Center, Randomized Study of Anti-CCR4 Monoclonal Antibody KW 0761 (mogamulizumab) Versus Vorinostat in Subjects with Previously Treated Cutaneous T-Cell Lymphoma (CTCL)

Summary

EudraCT number	2012-004766-17
Trial protocol	IT ES NL DK GB DE
Global end of trial date	17 February 2021

Results information

Result version number	v1 (current)
This version publication date	04 March 2022
First version publication date	04 March 2022

Trial information

Trial identification

Sponsor protocol code	0761-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01728805
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kyowa Kirin Inc.
Sponsor organisation address	Kyowa Kirin, 212 Carnegie Center, suite 400, Princeton, United States, 08540
Public contact	Clinical Trial Information, Kyowa Kirin Inc., +1 6099191100, kkd.clintrial.82@kyowakirin.com
Scientific contact	Clinical Trial Information, Kyowa Kirin Inc., +1 6099191100, kkd.clintrial.82@kyowakirin.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	02 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 March 2017
Global end of trial reached?	Yes
Global end of trial date	17 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the progression free survival of KW-0761 versus vorinostat for subjects with relapsed or refractory Cutaneous T-Cell Lymphoma (CTCL).

Protection of trial subjects:

The study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated guideline E6 - Good Clinical Practice (GCP) and any applicable national and local laws and regulations. Subjects were provided with written and oral information about the study (aims, methods, anticipated benefits, potential hazards and insurance arrangements). No procedures were conducted until informed consent was provided. The protocol included wording for the treatment of skin rash and hypersensitivity-like reactions (wording regarding premedication prior to KW-0761 infusion was also included in the protocol).

Background therapy: -

Evidence for comparator:

The comparator vorinostat (Zolinza) is approved in the USA, an ICH country, for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.

Actual start date of recruitment	28 November 2012
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	United States: 201
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Japan: 15
Country: Number of subjects enrolled	Switzerland: 4
Worldwide total number of subjects	372
EEA total number of subjects	136

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)	188
From 65 to 84 years	167
85 years and over	17

Subject disposition

Recruitment

Recruitment details:

Recruitment began in November 2012 and ended in December 2015.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participate in the trial. Subjects that met all inclusion/exclusion criteria as per protocol were eligible for entry into the study. A total of 464 patients were screened across 66 sites, of which 372 were randomized at 61 sites.

Period 1

Period 1 title	Randomized
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Mogamulizumab (KW-0761)

Arm description:

anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab)

Arm type	Experimental
Investigational medicinal product name	Mogamulizumab
Investigational medicinal product code	KW-0761
Other name	POTELIGEO®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.0 mg/kg weekly x 4 in cycle 1 then every other week until progression

Arm title	Vorinostat

Arm description:

Vorinostat

Arm type	Active comparator
Investigational medicinal product name	Vorinostat
Investigational medicinal product code	
Other name	ZOLINZA®
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

vorinostat 400 mg once daily

Number of subjects in period 1	Mogamulizumab (KW-0761)	Vorinostat
Started	186	186
Completed	184	186
Not completed	2	0
Consent withdrawn by subject	2	-

Period 2

Period 2 title	Crossover
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Vorinostat Original then Crossover to mogamulizumab

Arm description:

Subjects who were randomized to vorinostat could be crossed over to receive mogamulizumab upon disease progression (documented progression in any compartment per CTCL response criteria) and with permission from the Medical Monitor.

Arm type	Experimental
Investigational medicinal product name	Mogamulizumab
Investigational medicinal product code	KW-0761
Other name	POTELIGEO®
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.0 mg/kg weekly x 4 in cycle 1 then every other week until progression

Number of subjects in period 2[1]	Vorinostat Original then Crossover to mogamulizumab
Started	138
Completed	135
Not completed	3
never dosed	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: If a patient successfully completed one cycle of treatment, they are considered to have completed the period. All subjects who crossed over from vorinostat successfully completed one cycle, so they completed that period before joining the crossover period.

Baseline characteristics

Reporting groups	
Reporting group title	Mogamulizumab (KW-0761)
Reporting group description: anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab)	
Reporting group title	Vorinostat
Reporting group description: Vorinostat	

Reporting group values	Mogamulizumab (KW-0761)	Vorinostat	Total
Number of subjects	186	186	372
Age categorical Units: Subjects			
Adults (18-64 years)	99	89	188
From 65-84 years	83	92	175
85 years and over	4	5	9
Age continuous Units: years			
arithmetic mean	62.8	63.3	
full range (min-max)	25 to 101	25 to 89	-
Gender categorical Units: Subjects			
Female	77	79	156
Male	109	107	216

End points

End points reporting groups

Reporting group title	Mogamulizumab (KW-0761)
Reporting group description: anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab)	
Reporting group title	Vorinostat
Reporting group description: Vorinostat	
Reporting group title	Vorinostat Original then Crossover to mogamulizumab
Reporting group description: Subjects who were randomized to vorinostat could be crossed over to receive mogamulizumab upon disease progression (documented progression in any compartment per CTCL response criteria) and with permission from the Medical Monitor.	

Primary: Progression Free Survival

End point title	Progression Free Survival
End point description: Progression was defined as follows, based on Olsen (2011): - Lymph nodes: ≥ 50% increase in SPD from baseline of lymph nodes, any new node > 1.5 cm in the long axis or > 1 cm in the short axis if 1-1.5 cm in the long axis that is proven to be N3 histologically, or > 50% increase from nadir in SPD of lymph nodes in those with PR - Skin: ≥ 25% increase in skin disease from baseline, new tumors (T3) in patients with T1, T2 or T4 only skin disease, or in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score - Blood: B0 to B2, > 50% increase from baseline and at least 5,000 neoplastic cells/µL36, or > 50% increase from nadir and at least 5,000 neoplastic cells/µL - Viscera: > 50% increase in size (SPD) of any organs involved at baseline, new organ involvement, or > 50% increase from nadir in the size (SPD) of any previous organ involvement in those with PR	
End point type	Primary
End point timeframe: From date of randomization at every visit until the date of first documented progression or date of death from any cause, whichever came first, assessed up to 36 months	

End point values	Mogamulizumab (KW-0761)	Vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186	186		
Units: percent				
number (confidence interval 95%)				
Rate (%) of Being Alive w/o Progression at 6 mos.	55.3 (47.1 to 62.6)	28.8 (21.6 to 36.3)		
Rate (%) of Being Alive w/o Progression at 12 mos.	38.3 (30.2 to 46.4)	15.3 (9.5 to 22.3)		
Rate (%) of Being Alive w/o Progression at 18 mos.	28.0 (19.8 to 36.8)	7.2 (2.7 to 14.5)		
Rate (%) of Being Alive w/o Progression at 24 mos.	14.1 (6.4 to 24.8)	7.2 (2.7 to 14.5)		
Rate (%) of Being Alive w/o Progression at 30 mos.	4.7 (0.5 to 17.7)	7.2 (2.7 to 14.5)		

Statistical analyses

Statistical analysis title	Mogamulizumab vs vorinostat
Comparison groups	Mogamulizumab (KW-0761) v Vorinostat
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided

Secondary: Overall Response Rate - All Subjects

End point title	Overall Response Rate - All Subjects

End point description:

The ORR was defined as the count of subjects who had a confirmed CR or PR, defined as documented CR or PR per Global Composite Response Score that was confirmed by a subsequent observation at least 4 weeks later. Overall Response Rate was determined based on the response in all compartments affected at baseline (lymph nodes, skin, peripheral blood, and viscera), referencing Olsen, 2011 as follows: Complete Response (CR) = complete disappearance of all clinical evidence of disease; Partial Response (PR) = regression of measurable disease; Stable Disease (SD) = failure to attain CR, PR, or PD; Progressive Disease (PD) = PD in any compartment; Relapse = recurrence of disease in prior CR in any compartment.

End point type	Secondary

End point timeframe:

at the end of cycle 1 (26-28 days), and then every other cycle in Year 1 (cycle 3, 5, 7, 9, 11, 13), and every 16 weeks (cycle 17, 21, etc.) in Year 2 and beyond until progression.

End point values	Mogamulizumab (KW-0761)	Vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	186[1]	186[2]		
Units: participants				
# of Patients Who Had Confirmed CR or PR	52	9		

Notes:

[1] - Intent-to-treat set: All patients randomized to treatment arm

[2] - Intent-to-treat set: All patients randomized to treatment arm

Statistical analyses

Statistical analysis title	Treatment Comparison (mogamulizumab vs placebo)
Comparison groups	Mogamulizumab (KW-0761) v Vorinostat
Number of subjects included in analysis	372
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.8
upper limit	33.1

Secondary: Quality of Life (QoL) Assessment - Skindex-29 Symptoms Scale Score

End point title	Quality of Life (QoL) Assessment - Skindex-29 Symptoms Scale Score

End point description:

Skindex-29 rates 29 items assessing 3 domains (emotions, symptoms, & functioning) on a linear scale from 0 (never) to all the time (100). Higher scores = higher impact of skin disease.

End point type	Secondary

End point timeframe:

Cycle 1, 3, and 5 (6 months)

End point values	Mogamulizumab (KW-0761)	Vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162[3]	171[4]		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Change in Skindex-29 Score: 6 Month Assessment	-12.6 (-15.94 to -9.29)	-6.0 (-9.39 to -2.52)		

Notes:

[3] - Number of subjects with values at baseline & specified post-baseline timepoints.

[4] - Number of subjects with values at baseline & specified post-baseline timepoints.

Statistical analyses

Statistical analysis title	Treatment Comparison (mogamulizumab vs vorinostat)
Comparison groups	Mogamulizumab (KW-0761) v Vorinostat

Number of subjects included in analysis	333
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0002 [6]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.14
upper limit	-3.19
Variability estimate	Standard error of the mean

Notes:

[5] - LS mean, SE, 95% CI and P-value are from MMRM with treatment, disease type, disease stage, and region as fixed effects and baseline score as a covariate. Adjusted P-value is calculated using Sidak method for the overall difference across time points through 6-month assessment (including End of Cycles 1, 3, and 5 time points only).

[6] - adjusted P-value 0.0008

Secondary: Quality of Life (QoL) Assessment - FACT-G Scale Score

End point title	Quality of Life (QoL) Assessment - FACT-G Scale Score

End point description:

FACT-G rates 27 items in 4 domains (physical well-being, social/family well-being, emotional well-being, functional well-being) on a 5-point scale from 0 (not at all) to 4 (very much). Higher scores = better QoL.

End point type	Secondary

End point timeframe:

Cycle 1, 3, and 5 (6 months)

End point values	Mogamulizumab (KW-0761)	Vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	167[7]	177[8]		
Units: score on a scale				
least squares mean (confidence interval 95%)				
FACT-G Score Change: 6-Month Assessment	4.6 (2.14 to 7.04)	-2.3 (-4.84 to 0.21)		

Notes:

[7] - Number of subjects with values at baseline & specified post-baseline timepoints.

[8] - Number of subjects with values at baseline & specified post-baseline timepoints.

Statistical analyses

Statistical analysis title	Treatment Comparison (mogamulizumab vs vorinostat)
Comparison groups	Mogamulizumab (KW-0761) v Vorinostat

Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.0001 [10]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.39
upper limit	9.54
Variability estimate	Standard error of the mean

Notes:

[9] - LS mean, SE, 95% CI and P-value are from MMRM with treatment, disease type, disease stage, and region as fixed effects and baseline score as a covariate. Adjusted P-value is calculated using Sidak method for the overall difference across time points through 6-month assessment (including End of Cycles 1, 3, and 5 time points only)

[10] - Adjusted P-value < 0.0001

Secondary: Quality of Life (QoL) Assessment - Eq-5D-3L Scale Score

End point title	Quality of Life (QoL) Assessment - Eq-5D-3L Scale Score

End point description:

EuroQoL lvl 3 (Eq-5D-3L) rates mobility, self-care, usual activities, pain/discomfort and anxiety/depression on 3 levels - no problems, some problems, extreme problems. Score is calculated using a set of item weights to derive a single score ranging from -0.109 to 1, with 1 representing full health.

End point type	Secondary

End point timeframe:

Cycle 1, 3, and 5

End point values	Mogamulizumab (KW-0761)	Vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	169[11]	174[12]		
Units: score on a scale				
least squares mean (confidence interval 95%)				
Change in EQ-5D-3L Score: 6-Month Assessment	0.06 (0.028 to 0.085)	0.02 (-0.008 to 0.052)		

Notes:

[11] - number of subjects with values at baseline and the specified post-baseline timepoints.

[12] - number of subjects with values at baseline and the specified post-baseline timepoints.

Statistical analyses

Statistical analysis title	Treatment Comparison (mogamulizumab vs vorinostat)
Comparison groups	Mogamulizumab (KW-0761) v Vorinostat

Number of subjects included in analysis	343
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 0.021 [14]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.005
upper limit	0.064
Variability estimate	Standard error of the mean

Notes:

[13] - LS mean, SE, 95% CI and P-value are from MMRM with treatment, disease type, disease stage, and region as fixed effects and baseline score as a covariate. Adjusted P-value is calculated using Sidak method for the overall difference across time points through 6-month assessment (including End of Cycles 1, 3, and 5 time points only).
[14] - Adjusted P-value 0.0814

Secondary: Overall Response Rate - Mycosis Fungoides Patients

End point title	Overall Response Rate - Mycosis Fungoides Patients

End point description:

The ORR was defined as the count of subjects who had a confirmed CR or PR, defined as documented CR or PR per Global Composite Response Score that was confirmed by a subsequent observation at least 4 weeks later. Overall Response Rate was determined based on the response in all compartments (lymph nodes, skin, peripheral blood, and viscera), referencing Olsen, 2011 as follows: Complete Response (CR) = complete disappearance of all clinical evidence of disease; Partial Response (PR) = regression of measurable disease; Stable Disease (SD) = failure to attain CR, PR, or PD; Progressive Disease (PD) = PD in any compartment; Relapse = recurrence of disease in prior CR in any compartment.

End point type	Secondary

End point timeframe:

at the end of cycle 1 (26-28 days), and then every other cycle in Year 1 (cycle 3, 5, 7, 9, 11, 13), and every 16 weeks (cycle 17, 21, etc.) in Year 2 and beyond until progression.

End point values	Mogamulizumab (KW-0761)	Vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	99		
Units: participants	22	7		

Statistical analyses

Statistical analysis title	Treatment Comparison (mogamulizumab vs vorinostat)
Comparison groups	Mogamulizumab (KW-0761) v Vorinostat

Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0042
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	27.4

Secondary: Overall Response Rate - Sezary Syndrome Patients

End point title	Overall Response Rate - Sezary Syndrome Patients

End point description:

The ORR was defined as the count of subjects who had a confirmed CR or PR, defined as documented CR or PR per Global Composite Response Score that was confirmed by a subsequent observation at least 4 weeks later. Overall Response Rate was determined based on the response in all compartments (lymph nodes, skin, peripheral blood, and viscera), referencing Olsen, 2011 as follows: Complete Response (CR) = complete disappearance of all clinical evidence of disease; Partial Response (PR) = regression of measurable disease; Stable Disease (SD) = failure to attain CR, PR, or PD; Progressive Disease (PD) = PD in any compartment; Relapse = recurrence of disease in prior CR in any compartment.

End point type	Secondary

End point timeframe:

at the end of cycle 1 (26-28 days), and then every other cycle in Year 1 (cycle 3, 5, 7, 9, 11, 13), and every 16 weeks (cycle 17, 21, etc.) in Year 2 and beyond until progression.

End point values	Mogamulizumab (KW-0761)	Vorinostat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	87		
Units: participants	30	2		

Statistical analyses

Statistical analysis title	Treatment Comparison (mogamulizumab vs vorinostat)
Comparison groups	Mogamulizumab (KW-0761) v Vorinostat
Number of subjects included in analysis	168
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)

Confidence interval	
level	95 %
sides	2-sided
lower limit	19.9
upper limit	48.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All subjects were assessed regularly for potential occurrence of adverse events from the time of signing the informed consent until 90 days after the last dose or initiation of alternative therapy

Adverse event reporting additional description:

The following tables are based on all subjects who received at least 1 partial dose of the assigned study agent. 2 subjects randomized to KW0761 arm withdrew consent prior to receiving 1st dose, bringing # from 186 to 184. 3 subjects crossed over from vorinostat to KW0761 but discontinued before receiving drug, bringing # from 138 to 135.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Mogamulizumab (KW-0761)

Reporting group description:

Subjects randomized to this group received anti-CCR4 monoclonal antibody KW-0761 (mogamulizumab) 1.0 mg/kg weekly x 4 in cycle 1 then every other week until progression

Reporting group title	Vorinostat

Reporting group description:

Subjects randomized to this group received vorinostat 400 mg once daily

Reporting group title	Vorinostat Original then Crossover to mogamulizumab

Reporting group description:

Subjects who were randomized to vorinostat could be crossed over to receive mogamulizumab upon disease progression and with permission from the Medical Monitor.

Serious adverse events	Mogamulizumab (KW-0761)	Vorinostat	Vorinostat Original then Crossover to mogamulizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	73 / 184 (39.67%)	47 / 186 (25.27%)	41 / 135 (30.37%)
number of deaths (all causes)	64	67	45
number of deaths resulting from adverse events	4	8	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
ADENOCARCINOMA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

BLADDER TRANSITIONAL CELL CARCINOMA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BOWEN'S DISEASE			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COLON CANCER			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
INFECTED NEOPLASM			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MALIGNANT MELANOMA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
MALIGNANT PLEURAL EFFUSION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
METASTASES TO LYMPH NODES			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYCOSIS FUNGOIDES			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
OVARIAN CANCER			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
SQUAMOUS CELL CARCINOMA			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-CELL LYMPHOMA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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			
AIR EMBOLISM			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
AORTIC STENOSIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMBOLISM			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
PHLEBITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
Surgical and medical procedures			

CARDIAC PACEMAKER REPLACEMENT			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 184 (0.00%)	2 / 186 (1.08%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST DISCOMFORT			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHEST PAIN			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEATH			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
DEVICE FAILURE			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DISEASE PROGRESSION			
subjects affected / exposed	4 / 184 (2.17%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
FACIAL PAIN			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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

FATIGUE			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
HYPOTHERMIA			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOCALISED OEDEMA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OEDEMA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	8 / 184 (4.35%)	1 / 186 (0.54%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	4 / 9	0 / 1	2 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
CONTRAST MEDIA ALLERGY			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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

DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
HYPERSENSITIVITY			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
Social circumstances			
SOCIAL STAY HOSPITALISATION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
Reproductive system and breast disorders			
OEDEMA GENITAL			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
BRONCHITIS CHRONIC			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
DYSPNOEA EXERTIONAL			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
HAEMOPTYSIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
INTERSTITIAL LUNG DISEASE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
PLEURAL EFFUSION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
PNEUMONITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 184 (0.00%)	5 / 186 (2.69%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
RESPIRATORY FAILURE			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
CONFUSIONAL STATE			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
DEPRESSION			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENTAL STATUS CHANGES			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEMUR FRACTURE			

subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFUSION RELATED REACTION			
subjects affected / exposed	3 / 184 (1.63%)	0 / 186 (0.00%)	4 / 135 (2.96%)
occurrences causally related to treatment / all	3 / 3	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LACERATION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
LOWER LIMB FRACTURE			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC FRACTURE			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
SUBDURAL HAEMATOMA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
SUBDURAL HAEMORRHAGE			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
VASCULAR ACCESS COMPLICATION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
CRANIOCEREBRAL INJURY			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA PECTORIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANGINA UNSTABLE			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CARDIAC FAILURE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LEFT VENTRICULAR HYPERTROPHY			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
MYOCARDITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
SUPRAVENTRICULAR TACHYCARDIA			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
ATRIOVENTRICULAR BLOCK SECOND DEGREE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
HYPERTENSIVE CARDIOMYOPATHY			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TACHYCARDIA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
Nervous system disorders			
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
HEPATIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METABOLIC ENCEPHALOPATHY			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MILLER FISHER SYNDROME			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
MONOPARESIS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
MOTOR DYSFUNCTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 184 (0.54%)	2 / 186 (1.08%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ANAEMIA HAEMOLYTIC AUTOIMMUNE			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
HAEMOLYTIC ANAEMIA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUTROPENIA			

subjects affected / exposed	0 / 184 (0.00%)	2 / 186 (1.08%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 184 (0.00%)	3 / 186 (1.61%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
LENS DISLOCATION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
RETINAL VEIN OCCLUSION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
ANAL FISTULA			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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

COLITIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC HAEMORRHAGE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
ILEITIS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
INGUINAL HERNIA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
LARGE INTESTINAL ULCER HAEMORRHAGE			

subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LIP SWELLING			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
STOMATITIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
Hepatobiliary disorders			
AUTOIMMUNE HEPATITIS			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLANGITIS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
CHOLECYSTITIS ACUTE			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATIC FAILURE			

subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEPATITIS ACUTE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	12 / 135 (8.89%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHOLECYSTITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
Skin and subcutaneous tissue disorders			
DERMATITIS EXFOLIATIVE			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DRUG ERUPTION			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PHOTOSENSITIVITY REACTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
PRURITUS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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 DISORDER			

subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
URTICARIA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ALOPECIA AREATA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
RASH			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITILIGO			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
RENAL FAILURE			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL FAILURE ACUTE			
subjects affected / exposed	2 / 184 (1.09%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RENAL IMPAIRMENT			

subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
URINARY RETENTION			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
Endocrine disorders			
AUTOIMMUNE THYROIDITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 184 (1.09%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
MONARTHRITIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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

MYALGIA			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MYOSITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
OSTEOARTHRITIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POLYMYOSITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
VERTEBRAL FORAMINAL STENOSIS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
Infections and infestations			
ABSCESS LIMB			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
APPENDICITIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ARTHRITIS BACTERIAL			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
ATYPICAL PNEUMONIA			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
BACTERAEMIA			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHITIS			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRONCHOPNEUMONIA			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CELLULITIS			
subjects affected / exposed	5 / 184 (2.72%)	6 / 186 (3.23%)	3 / 135 (2.22%)
occurrences causally related to treatment / all	3 / 5	0 / 6	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CYTOMEGALOVIRUS INFECTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
ENDOCARDITIS			

subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
ENTEROVIRUS INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPSTEIN-BARR VIRUS INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTROENTERITIS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
HERPES SIMPLEX			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HERPES ZOSTER			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFLUENZA			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
OSTEOMYELITIS			
subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OTITIS EXTERNA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIORBITAL CELLULITIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOCYSTIS JIROVECI PNEUMONIA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
PNEUMONIA			
subjects affected / exposed	4 / 184 (2.17%)	2 / 186 (1.08%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	4 / 5	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
PNEUMONIA INFLUENZAL			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
PNEUMONIA LEGIONELLA			

subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
PNEUMONIA PNEUMOCOCCAL			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
RHINOVIRUS INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	3 / 184 (1.63%)	5 / 186 (2.69%)	2 / 135 (1.48%)
occurrences causally related to treatment / all	3 / 4	0 / 5	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 1	0 / 1
SEPSIS SYNDROME			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
SEPTIC EMBOLUS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
SEPTIC SHOCK			

subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
SKIN INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	4 / 186 (2.15%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL ABSCESS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL BACTERAEMIA			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STAPHYLOCOCCAL INFECTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
STAPHYLOCOCCAL SEPSIS			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPERINFECTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	2 / 186 (1.08%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			

subjects affected / exposed	2 / 184 (1.09%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION BACTERIAL			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIRAL INFECTION			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
UROSEPSIS			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 184 (0.54%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
GOUT			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (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
HYPERCALCAEMIA			

subjects affected / exposed	3 / 184 (1.63%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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
HYPOALBUMINAEMIA			
subjects affected / exposed	1 / 184 (0.54%)	0 / 186 (0.00%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
HYPOKALAEMIA			
subjects affected / exposed	0 / 184 (0.00%)	2 / 186 (1.08%)	0 / 135 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	1 / 135 (0.74%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
METABOLIC ACIDOSIS			
subjects affected / exposed	0 / 184 (0.00%)	1 / 186 (0.54%)	0 / 135 (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

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

Non-serious adverse events	Mogamulizumab (KW-0761)	Vorinostat	Vorinostat Original then Crossover to mogamulizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	179 / 184 (97.28%)	185 / 186 (99.46%)	129 / 135 (95.56%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	9 / 135 (6.67%)
occurrences (all)	0	0	14

Vascular disorders			
HYPERTENSION			
subjects affected / exposed	18 / 184 (9.78%)	25 / 186 (13.44%)	0 / 135 (0.00%)
occurrences (all)	39	28	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	10 / 184 (5.43%)	28 / 186 (15.05%)	14 / 135 (10.37%)
occurrences (all)	12	34	22
CHILLS			
subjects affected / exposed	13 / 184 (7.07%)	14 / 186 (7.53%)	8 / 135 (5.93%)
occurrences (all)	17	15	8
FATIGUE			
subjects affected / exposed	44 / 184 (23.91%)	70 / 186 (37.63%)	15 / 135 (11.11%)
occurrences (all)	56	77	24
OEDEMA PERIPHERAL			
subjects affected / exposed	28 / 184 (15.22%)	27 / 186 (14.52%)	16 / 135 (11.85%)
occurrences (all)	35	38	21
PYREXIA			
subjects affected / exposed	33 / 184 (17.93%)	12 / 186 (6.45%)	17 / 135 (12.59%)
occurrences (all)	38	12	30
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	7 / 135 (5.19%)
occurrences (all)	0	0	9
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	20 / 184 (10.87%)	16 / 186 (8.60%)	10 / 135 (7.41%)
occurrences (all)	23	19	12
DYSPNOEA			
subjects affected / exposed	10 / 184 (5.43%)	7 / 186 (3.76%)	7 / 135 (5.19%)
occurrences (all)	14	8	9
OROPHARYNGEAL PAIN			
subjects affected / exposed	11 / 184 (5.98%)	5 / 186 (2.69%)	9 / 135 (6.67%)
occurrences (all)	11	7	10
Psychiatric disorders			
DEPRESSION			

subjects affected / exposed	11 / 184 (5.98%)	6 / 186 (3.23%)	0 / 135 (0.00%)
occurrences (all)	11	6	0
INSOMNIA			
subjects affected / exposed	17 / 184 (9.24%)	14 / 186 (7.53%)	0 / 135 (0.00%)
occurrences (all)	17	14	0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	12 / 184 (6.52%)	8 / 186 (4.30%)	13 / 135 (9.63%)
occurrences (all)	15	12	18
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	10 / 184 (5.43%)	12 / 186 (6.45%)	14 / 135 (10.37%)
occurrences (all)	16	19	21
BLOOD CREATININE INCREASED			
subjects affected / exposed	6 / 184 (3.26%)	52 / 186 (27.96%)	0 / 135 (0.00%)
occurrences (all)	10	59	0
PLATELET COUNT DECREASED			
subjects affected / exposed	4 / 184 (2.17%)	19 / 186 (10.22%)	0 / 135 (0.00%)
occurrences (all)	6	22	0
WEIGHT DECREASED			
subjects affected / exposed	11 / 184 (5.98%)	32 / 186 (17.20%)	10 / 135 (7.41%)
occurrences (all)	15	35	10
WEIGHT INCREASED			
subjects affected / exposed	15 / 184 (8.15%)	2 / 186 (1.08%)	7 / 135 (5.19%)
occurrences (all)	17	2	7
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	3 / 184 (1.63%)	11 / 186 (5.91%)	10 / 135 (7.41%)
occurrences (all)	3	11	13
INFUSION RELATED REACTION			
subjects affected / exposed	61 / 184 (33.15%)	0 / 186 (0.00%)	51 / 135 (37.78%)
occurrences (all)	86	0	59
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	12 / 184 (6.52%)	19 / 186 (10.22%)	8 / 135 (5.93%)
occurrences (all)	13	20	12

DYSGEUSIA			
subjects affected / exposed	8 / 184 (4.35%)	55 / 186 (29.57%)	0 / 135 (0.00%)
occurrences (all)	9	59	0
HEADACHE			
subjects affected / exposed	25 / 184 (13.59%)	27 / 186 (14.52%)	17 / 135 (12.59%)
occurrences (all)	37	33	33
PARAESTHESIA			
subjects affected / exposed	5 / 184 (2.72%)	14 / 186 (7.53%)	8 / 135 (5.93%)
occurrences (all)	5	16	10
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	21 / 184 (11.41%)	20 / 186 (10.75%)	9 / 135 (6.67%)
occurrences (all)	40	25	10
NEUTROPENIA			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	7 / 135 (5.19%)
occurrences (all)	0	0	8
THROMBOCYTOPENIA			
subjects affected / exposed	22 / 184 (11.96%)	58 / 186 (31.18%)	11 / 135 (8.15%)
occurrences (all)	37	87	53
Eye disorders			
DRY EYE			
subjects affected / exposed	7 / 184 (3.80%)	11 / 186 (5.91%)	0 / 135 (0.00%)
occurrences (all)	7	11	0
VISION BLURRED			
subjects affected / exposed	8 / 184 (4.35%)	12 / 186 (6.45%)	7 / 135 (5.19%)
occurrences (all)	9	14	7
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	9 / 184 (4.89%)	22 / 186 (11.83%)	7 / 135 (5.19%)
occurrences (all)	10	25	7
ABDOMINAL PAIN UPPER			
subjects affected / exposed	2 / 184 (1.09%)	11 / 186 (5.91%)	0 / 135 (0.00%)
occurrences (all)	2	13	0
CONSTIPATION			
subjects affected / exposed	23 / 184 (12.50%)	34 / 186 (18.28%)	15 / 135 (11.11%)
occurrences (all)	28	38	15
DIARRHOEA			

subjects affected / exposed	48 / 184 (26.09%)	115 / 186 (61.83%)	24 / 135 (17.78%)
occurrences (all)	68	182	35
DRY MOUTH			
subjects affected / exposed	4 / 184 (2.17%)	17 / 186 (9.14%)	0 / 135 (0.00%)
occurrences (all)	5	17	0
DYSPEPSIA			
subjects affected / exposed	2 / 184 (1.09%)	11 / 186 (5.91%)	0 / 135 (0.00%)
occurrences (all)	2	11	0
NAUSEA			
subjects affected / exposed	30 / 184 (16.30%)	78 / 186 (41.94%)	11 / 135 (8.15%)
occurrences (all)	39	100	15
STOMATITIS			
subjects affected / exposed	11 / 184 (5.98%)	2 / 186 (1.08%)	0 / 135 (0.00%)
occurrences (all)	18	3	0
VOMITING			
subjects affected / exposed	13 / 184 (7.07%)	24 / 186 (12.90%)	0 / 135 (0.00%)
occurrences (all)	14	34	0
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	14 / 184 (7.61%)	35 / 186 (18.82%)	9 / 135 (6.67%)
occurrences (all)	14	35	9
DRUG ERUPTION			
subjects affected / exposed	46 / 184 (25.00%)	2 / 186 (1.08%)	37 / 135 (27.41%)
occurrences (all)	87	3	56
INTERTRIGO			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	7 / 135 (5.19%)
occurrences (all)	0	0	12
RASH			
subjects affected / exposed	9 / 184 (4.89%)	10 / 186 (5.38%)	11 / 135 (8.15%)
occurrences (all)	13	12	15
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	15 / 184 (8.15%)	11 / 186 (5.91%)	17 / 135 (12.59%)
occurrences (all)	17	18	23
BACK PAIN			

subjects affected / exposed	18 / 184 (9.78%)	9 / 186 (4.84%)	11 / 135 (8.15%)
occurrences (all)	22	10	15
MUSCLE SPASMS			
subjects affected / exposed	10 / 184 (5.43%)	29 / 186 (15.59%)	0 / 135 (0.00%)
occurrences (all)	11	50	0
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	7 / 135 (5.19%)
occurrences (all)	0	0	7
MYALGIA			
subjects affected / exposed	12 / 184 (6.52%)	8 / 186 (4.30%)	8 / 135 (5.93%)
occurrences (all)	14	10	9
PAIN IN EXTREMITY			
subjects affected / exposed	14 / 184 (7.61%)	11 / 186 (5.91%)	13 / 135 (9.63%)
occurrences (all)	19	18	14
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 184 (0.00%)	0 / 186 (0.00%)	10 / 135 (7.41%)
occurrences (all)	0	0	16
FOLLICULITIS			
subjects affected / exposed	14 / 184 (7.61%)	4 / 186 (2.15%)	13 / 135 (9.63%)
occurrences (all)	19	4	19
NASOPHARYNGITIS			
subjects affected / exposed	14 / 184 (7.61%)	16 / 186 (8.60%)	12 / 135 (8.89%)
occurrences (all)	25	23	17
ORAL CANDIDIASIS			
subjects affected / exposed	11 / 184 (5.98%)	1 / 186 (0.54%)	0 / 135 (0.00%)
occurrences (all)	15	1	0
SKIN INFECTION			
subjects affected / exposed	17 / 184 (9.24%)	13 / 186 (6.99%)	0 / 135 (0.00%)
occurrences (all)	30	18	0
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	21 / 184 (11.41%)	10 / 186 (5.38%)	13 / 135 (9.63%)
occurrences (all)	30	11	27
URINARY TRACT INFECTION			

subjects affected / exposed	15 / 184 (8.15%)	14 / 186 (7.53%)	8 / 135 (5.93%)
occurrences (all)	20	20	12
CELLULITIS			
subjects affected / exposed	6 / 184 (3.26%)	10 / 186 (5.38%)	7 / 135 (5.19%)
occurrences (all)	6	12	10
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	16 / 184 (8.70%)	45 / 186 (24.19%)	0 / 135 (0.00%)
occurrences (all)	17	50	0
HYPERGLYCAEMIA			
subjects affected / exposed	15 / 184 (8.15%)	14 / 186 (7.53%)	0 / 135 (0.00%)
occurrences (all)	29	29	0
HYPOKALAEMIA			
subjects affected / exposed	11 / 184 (5.98%)	13 / 186 (6.99%)	0 / 135 (0.00%)
occurrences (all)	16	19	0
HYPOMAGNESAEMIA			
subjects affected / exposed	10 / 184 (5.43%)	3 / 186 (1.61%)	0 / 135 (0.00%)
occurrences (all)	12	3	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2012	To incorporate changes requested by the FDA on 02Jul2012. - deleted Table 3 Study Procedures: KW-0761 Monthly Maintenance Schedule - revised Section 5.2.1.3 Duration of Treatment to specify same follow up period for both treatment arms - added wording to Section 5.2.1.5.1 Treatment of Hypersensitivity-Like Reactions to ensure patient safety - revised Section 5.2.2.3 Duration of Treatment to specify same follow up period for both treatment arms - added Section 7.1.2 Preparation of Dose - revised Section 9.3 Analyses of Efficacy Data to further specify follow up period for survival
19 February 2013	- To clarify the time points for the collection of adverse events, T-cell counts, and samples for thyroid function tests - to clarify that vorinostat is not currently approved by the European Medicines Agency for the treatment of cutaneous T-cell lymphoma and would be considered an investigational medicinal product within Europe, include a summary of clinical efficacy and safety for KW-0761 based on Edition 8 of the Investigator's Brochure, provide the rationale to allow subjects to continue in treatment as the time required to demonstrate a response to immune-based therapies may be more prolonged - Visual Analog Scale (i.e., a continuous scale), has been replaced by the Likert scale (i.e., a numbered scale) for the assessment of pruritis - order of secondary objectives has been modified to reflect the importance of quality of life data and to specify the exploratory objectives of overall survival and KW 0761 exposure-response relationships - Modify the Inclusion/Exclusion Criteria, based primarily on Investigator feedback - Add sites in Europe to facilitate accrual - Specify the permissible dosing interval for KW-0761 administration during the first treatment cycle - Allow subjects with progressive disease in one disease compartment to continue to be treated on study, after consultation with Medical Monitor, for a period of up to 8 weeks - Collect serum samples for analysis of anti-KW-0761 antibodies in subjects who experience an infusion reaction and to clarify infusion duration - Clarify that body weight changes of ≥ 10%, relative to Day 1, requires dose adjustment - Lengthen the Screening period to better reflect the time required to obtain the results prior to Day 1 - Implement changes in the statistical analysis to improve the probability of success for achieving the primary objective - A Data Safety Monitoring Board has been added to oversee subject safety in the trial - administrative/personnel changes - typographical/grammatical changes

03 April 2013	- To prevent a subject from being removed from the study prematurely when the definition of PD or relapse is met but the clinical impression is questionable, in accordance with published international response criteria.10 In this case, after consultation with Medical Monitor, the investigator may continue to treat a subject for at least 4 weeks. Subjects in frank or obvious PD in any compartment should be discontinued from protocol therapy - To update the definition of disease progression in the subset of patients where the clinical impression is questionable - To update the response criteria based on the current international response criteria in Mycosis Fungoides and Sézary Syndrome - administrative/personnel changes - typographical corrections
14 November 2013	- To describe the treatment options that are available for patients in Japan - To allow Japanese subjects who are at least 20 years of age to participate in this study - To clarify that a skin biopsy must be performed on site, if necessary, to provide a histologically confirmed diagnosis of MF or SS within 3 months of the Pretreatment Visit in order to meet the study entry criterion - To modify the definition of postmenopausal female to conform with the International Conference on Harmonisation's "Guidance for Industry M3(R2)" - To correct the maximum prostate specific antigen level permitted in subjects with localized cancer of the prostate - To allow patients with limited prior exposure to vorinostat to be permitted to participate in this study, after discussion with the Medical Monitor - To consider allowing subjects treated with vorinostat who have rapidly progressive malignant disease to cross over to treatment with KW-0761 prior to 8 weeks, with the approval of the Medical Monitor or designee - To permit the administration of the influenza vaccine - To specify that treatment with KW-0761 will be stopped if the subject experiences an infusion-related reaction with a severity of ≥ Grade 2 upon re-challenge or true hypersensitivity - To clarify the criteria for determining response in the lymph nodes - 4 additional serum samples will be drawn between 6 and 8 hours, and at 6-8, 24, 48, and 96 hours after the first infusion on Day 1/Cycle 1 in ~10 subjects - To provide the region-specific study drug packaging and labelling for Japan - To provide a description of the vorinostat capsules supplied by the Sponsor - To remove the fixed time point assessments (every 6 months) summaries for the key secondary endpoints

05 March 2014	- To provide updated safety information for KW-0761 based on IB 10 - To clarify which subjects require an additional biopsy for diagnosis within 3 months of the Pre-treatment Visit - To clarify that both relapsed and refractory patients are eligible to participate and that patients whose prior therapy includes only psoralen plus ultraviolet light therapy (PUVA) are not eligible - Add up to 10 sites in Australia - To allow subjects with rapid disease progression to crossover to treatment with KW 0761 prior to the 2-week washout period - To record medication taken during follow-up if used to treat an AE - To recommend premedication with acetaminophen or paracetamol orally and diphenhydramine 50 mg iv (or equivalent anti-histamine) for all subjects before the first KW-0761 infusion - To specify that any subject who experiences a Grade 4 infusion reaction is to be discontinued - To specify that subjects who require systemic steroid therapy to treat a severe skin rash should be discontinued - To specify that partial thromboplastin time or activated partial thromboplastin time testing may be performed - To clarify that the determination of KW-0761 concentration is part of the assessment of immunogenicity - To reduce the frequency of CT scans from every 8 weeks to every 16 weeks after the first year of treatment - To add an additional skin biopsy for the determination of CCR4 expression for subjects assigned to vorinostat who cross over to treatment with KW-0761 - To specify that paraffin blocks or fresh tissue samples are preferred for determination of CCR4 expression - To clarify that the optional skin biopsies will be submitted for pathology to the study site’s local lab - an additional 4 PK samples will be collected after the first dose at selected sites, and subjects who crossover to KW-0761 will also undergo the collection of serum samples
06 March 2015	- To change the medical monitor for European study sites and add the Medical Monitor for Australia - To update the approval status of mogamulizumab in Japan - To allow subjects who develop large cell transformation while on vorinostat to cross over to KW-0761 - To clarify the criteria for continuation of treatment in cases where the PD or relapse criteria is met but the clinical impression is questionable - To clarify that subjects in either treatment arm should not receive live or live attenuated vaccines due to the potential for immunosupression - To harmonize the criteria for removal from the study with the criteria for discontinuation - To clarify that the baseline measurements for cross-over subjects are those documented closest to and before the first KW-0761 infusion - To clarify that subjects who have an equivocal increase in mSWAT score may remain on treatment until subsequent measurement to confirm progression or relapse - To clarify the size criteria for assessing nodes as sites of disease - To clarify inconsistencies in response categories - To specify that if PD leading to discontinuation is documented, the overall global response should be completed at that time - To make the follow-up for subjects achieving a complete response consistent with the frequency of CT scans - To clarify that Packaging Coordinators, Inc. will distribute the study drug to the pharmacies at the study sites in Australia - To update the publication policy - To correct typographical errors and inconsistencies between sections of the protocol

09 March 2016	- The text in Section 4.2 has been modified to indicate that the primary analysis will be conducted when 255 total progression-free survival (PFS) events have been observed or at 24 months after the last randomized subject's first dose, whichever comes first - The description of planned exposure-response analyses were updated to reflect the current plan - Consistent with the modified ISCL/EORTC response criteria in MF/SS (Olsen, 2011), additional details were added to Appendix 1 regarding T4 definition for SS subjects and the interpretation of flow cytometry results - For consistency, references to "24 months after the last subject is dosed" have been clarified to indicate 24 months after the last randomized subject's first dose - To clarify footnotes in the Study Procedures tables relating to follow-up for disease progression and survival status after discontinuation of treatment; tables were updated to clarify that subject discontinuation may occur at any time (not necessarily associated with a specific study visit) - To clarify that skin rash should only be reported as an AE/SAE if initial workup indicates that it is not lymphoma - To clarify the timing of global composite response assessments during the first year of treatment and thereafter - Several footnotes were modified to be consistent with the the modified ISCL/EORTC response criteria in MF/SS (Olsen, 2011) - The procedures for independent review of progression (Section 7.2.4.1) were clarified - To clarify that crossover subjects are eligible to have additional blood samples drawn for pharmacokinetic analysis after receiving their first dose of KW-0761
20 January 2017	- a note was added to Section 3.2 (Inclusion Criteria) to specify that for subjects ongoing as of this amendment, women of child-bearing potential (and male subjects and their female partners of child bearing potential) should use effective methods of contraception for 6 months after the last dose of KW-0761 - Section 5.5 (Criteria for Removal from Study) was updated to specify that pregnancies occurring up to 6 months after the last dose of study medication must be reported to the Sponsor - Section 7 (Study Measurements) was updated to specify that pathology reports relevant to confirmation of the diagnosis of CTCL (mycosis fungoides or Sezary syndrome) for all enrolled subjects should be provided to the Sponsor - Section 7.5 (Follow-up) was updated to include reporting of transplant information including associated AE/SAEs and concomitant medications for any subjects who undergo HSCT after receiving KW 0761 - It is anticipated that some subjects will be continuing to receive study treatment at the time of the primary efficacy analysis. A new section (Section 7.7) was added to the protocol to allow for these subjects to continue study treatment and, pending notification by the Sponsor, to be followed according to institutional standard of care for subsequent assessments of treatment efficacy. - Adverse Event Contacts: Change in personnel and contact information noted - Company name change
20 April 2018	In order to provide clarification as to the management of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), the following statement has been added to Section 5.2.1.8 and referenced in Section 5.5: - Patients should be closely monitored for symptoms or signs that suggest SJS or TEN. If they occur, mogamulizumab should be interrupted and treatment should not restart unless SJS or TEN is ruled out and cutaneous reaction has resolved to Grade 1 or less. Additional changes to the protocol have been made as follows: - Change in personnel and contact information noted. - Company address change.

31 May 2018	A new section (Section 7.8) was added to the protocol to specify procedures to be followed for subjects who are ongoing in the study at the time of initial marketing authorization. These procedures should be implemented upon notification by the Sponsor. - For subjects who are continuing to receive KW-0761, the Sponsor will continue to supply study drug until KW-0761 becomes commercially available (reimbursable) in the country/region of the study site or until KW-0761 is not approved for marketing for the indication and regimen under study in the country/region of the study site. - For all ongoing subjects, i.e., subjects who are continuing to receive KW-0761 or who are in safety or survival follow-up at the time of initial marketing authorization, changes in study procedures and data collection are described.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported