Clinical trial results:
A PHASE II, MULTICENTER, OPEN-LABEL TRIAL EVALUATING THE ACTIVITY AND TOLERABILITY OF ROMIDEPSIN (DEPSIPEPTIDE, FK228) IN PROGRESSIVE OR RELAPSED PERIPHERAL T-CELL LYMPHOMA FOLLOWING PRIOR SYSTEMIC THERAPY

Summary

EudraCT number	2006-006228-21
Trial protocol	DE CZ FR ES SE GB IT
Global end of trial date	17 May 2018

Results information

Result version number	v1 (current)
This version publication date	31 May 2019
First version publication date	31 May 2019

Trial information

Trial identification

Sponsor protocol code	GPI-06-0002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00426764
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Celgene Corporation
Sponsor organisation address	86 Morris Avenue, Summit, NJ, United States, 07901
Public contact	Clinical Trial Disclosure, Celgene Corporation, ClinicalTrialDisclosure@celgene.com
Scientific contact	Jeffrey Jones, Celgene, 1 9086739686, jejones@celgene.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	17 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate the activity of romidepsin in patients with progressive or relapsed PTCL following prior systemic therapy. The primary efficacy parameter is the rate of complete response, defined as the proportion of patients with complete response (CR) and unconfirmed complete response [CR(u)] according to the IWC for responses assessment for non-Hodgkin's lymphomas (NHL).

Protection of trial subjects:

This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2007
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	Australia: 15
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	United States: 61
Worldwide total number of subjects	131
EEA total number of subjects	54

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)	81
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening tests were to be obtained within 2 weeks prior to study entry (defined as first dose of romidepsin, unless otherwise indicated).

Period 1

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

Arms

Arm title	Romidepsin

Arm description:

Subjects received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Arm type	Experimental
Investigational medicinal product name	Romidepsin
Investigational medicinal product code	
Other name	ISTODAX, Depsipeptide, FK228
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Romidepsin intravenously (through a vein) over 4 hours on Days 1, 8 and 15 of each 28-day cycle.

Number of subjects in period 1	Romidepsin
Started	131
Discontinued Prior to or During Cycle 6	98
Discontinued at End of or After Cycle 6	33
Completed	0
Not completed	131
Physician decision	6
Adverse Event	24
Not Specfied	1
Death	1
Progressive Disease	83
Withdrawal by Patient	4
Other Reasons (Miscellaneous)	10

Compassionate Use	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Romidepsin
Reporting group description:	
Subjects received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.	

Reporting group values	Romidepsin	Total	
Number of subjects	131	131	
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	59.4		
standard deviation	± 12.83	-	
Gender categorical			
Units: Subjects			
Female	42	42	
Male	89	89	
PTCL Subtype Based on Central Diagnosis			
ALK-1=anaplastic lymphoma kinase; ALCL=anaplastic large cell lymphoma			
Units: Subjects			
PTCL Unspecified (NOS)	69	69	
Angioimmunoblastic T-cell lymphoma (AITL)	27	27	
ALK-1 negative ALCL	21	21	
Enteropathy-type T-cell lymphoma	6	6	
Subcutaneous panniculitis-like T-cell lymphoma	3	3	
ALK-1 positive ALCL	1	1	
Cutaneous γδ T-cell lymphoma	1	1	
Extranodal NK/T cell lymphoma nasal type	1	1	
Transformed mycosis fungoides	1	1	
Not in Subject Analysis Set	1	1	
Race			
Units: Subjects			
White	117	117	
Black	7	7	
Asian	3	3	
Other	4	4	
Eastern Cooperative Oncology Group Performance Status [1]			
The ECOG scale is as follows: Grade 0: Fully active, able to carry on all pre-disease activities without restriction; Grade 1: Restricted in physically strenuous activity, ambulatory and able to carry out work of a light nature; Grade 2: Ambulatory and capable of all self-care but unable to work. Up and about			

more than 50% of waking hours; Grade 3: Capable of only limited self-care, confined to bed or chair > 50% of waking hours; Grade 4: Completely disabled. Cannot carry on any self-care. Confined to bed or Chair.			
Units: Subjects			
Grade 0	46	46	
Grade 1	67	67	
Grade 2	17	17	
Missing	1	1	
Body Surface Area (BSA)			
subjects with a Baseline measurement (n=128)			
Units: m^2			
arithmetic mean	1.84		
standard deviation	± 0.2348	-	
Duration of peripheral T-cell lymphoma (PTCL)			
Units: years			
arithmetic mean	2.268		
standard deviation	± 2.6654	-	

End points

End points reporting groups

Reporting group title	Romidepsin

Reporting group description:

Subjects received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Subject analysis set title	Histopathologically-Confirmed Population
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with central histologic confirmation of peripheral T-cell lymphoma (PTCL).

Subject analysis set title	Missing ECOG
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with a missing best on study ECOG performance score, who received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Subject analysis set title	Best ECOG = 0
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with a best on study ECOG performance score of 0, who received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Subject analysis set title	Best ECOG = 1
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with a best on study ECOG performance score of 1, who received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Subject analysis set title	Best ECOG = 2
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with a best on study ECOG performance score of 2, who received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Subject analysis set title	Best ECOG = 3
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with a best on study ECOG performance score of 3, who received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Subject analysis set title	Best ECOG = 4
Subject analysis set type	Full analysis

Subject analysis set description:

Subjects with a best on study ECOG performance score of 4, who received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin. The planned duration of study therapy was 6 cycles. Subjects who responded could continue beyond 6 cycles until disease progression or other withdrawal criteria were met. For subjects treated for 12 or more cycles, maintenance dosing (2 doses per cycle) was permitted.

Primary: Percentage of Subjects With a Complete Response According to the International Workshop Response Criteria (IWC) for Non-Hodgkin's Lymphomas (NHL) Assessed by an Independent Review Committee

End point title	Percentage of Subjects With a Complete Response According to the International Workshop Response Criteria (IWC) for Non-Hodgkin's Lymphomas (NHL) Assessed by an Independent Review Committee[1]

End point description:

Complete Response (CR): >75% decrease in size aggregate of nodal index lesions (large and small), complete disappearance of extranodal and non-index lesions; total disappearance of clinical disease including skin involvement; disease-related signs and symptoms, normalization of biochemical abnormalities and reduction in size of spleen or liver so no longer palpable. Unconfirmed CR: all above criteria except all nodal index lesions must have regressed >75% in the sum of the product diameters (SPD) from baseline. Individual nodes previously confluent must have regressed by >75% in their SPD.

End point type	Primary

End point timeframe:

Response was assessed after every 2 cycles of treatment and at completion of therapy, up until 30 September 2012 (data cutoff for analysis). Maximum duration on study was 1931 days.

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: Descriptive statistics are presented, per protocol.

End point values	Histopathologically-Confirmed Population			
Subject group type	Subject analysis set			
Number of subjects analysed	130			
Units: percentage of subjects				
number (confidence interval 95%)	15.4 (9.7 to 22.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Disease Response

End point title	Duration of Objective Disease Response

End point description:

Duration of response was defined as the number of days from the date of the first disease response (Complete, Unconfirmed Complete or Partial Response) until the date of progression and was determined using Kaplan-Meier product-limit estimates. Progression was defined as: a ≥50% increase from the nadir in the individual sum of the products of the diameters of any index lesion; the reappearance of pathology, enlargement of liver/spleen, or unequivocal progression of non-measurable disease or appearance of any new lesions. Histopathologically-Confirmed Population with an objective response. Censoring for patients who did not have a date of progression was conducted based on last assessment reported for the patient.

End point type	Secondary

End point timeframe:

Response was assessed after every 2 cycles of treatment and at completion of therapy, up until 30 September 2012 (data cutoff for analysis). Maximum duration on study was 1931 days.

End point values	Romidepsin	Histopathologically-Confirmed Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	34	34[2]		
Units: days				
median (confidence interval 95%)	999999 (353 to 999999)	999999 (353 to 999999)		

Notes:

[2] - 999999=not estimable due to the low number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Complete Disease Response

End point title	Duration of Complete Disease Response

End point description:

Duration of response was defined as the number of days from the date of the first disease response (Complete or Unconfirmed Complete) until the date of progression and was determined using Kaplan-Meier product-limit estimates. Progression was defined as: a ≥50% increase from the nadir in the individual sum of the products of the diameters of any index lesion; the reappearance of pathology, enlargement of liver/spleen, or unequivocal progression of non-measurable disease or appearance of any new lesions. Histopathologically-Confirmed Population with a complete response. Censoring for subjects who did not have a date of progression was conducted based on last assessment reported for the subject.

End point type	Secondary

End point timeframe:

Response was assessed after every 2 cycles of treatment and at completion of therapy, up until 30 September 2012 (data cutoff for analysis). Maximum duration on study was 1931 days.

End point values	Romidepsin	Histopathologically-Confirmed Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	20	20[3]		
Units: days				
median (confidence interval 95%)	999999 (500 to 999999)	999999 (500 to 999999)		

Notes:

[3] - 999999=not estimable due to the low number of events

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Disease Response

End point title	Percentage of Participants With Objective Disease Response

End point description:

Objective disease response was defined as patients with a Complete Response, Unconfirmed Complete Response or a Partial Response (PR) according to the IWC 1999 assessed by an independent review committee: CR, Cru defined above, PR defined as ≥50% decrease in size of 6 largest dominant nodes and/or nodal masses & extranodal index lesions and no increase of non-index lesions, liver, or spleen; no new sites of disease evident; skin lesions decreased by ≥50%.

End point type	Secondary

End point timeframe:

Response was assessed after every 2 cycles of treatment and at completion of therapy, up until 30 September 2012 (data cutoff for analysis). Maximum duration on study was 1931 days.

End point values	Histopathologically-Confirmed Population			
Subject group type	Subject analysis set			
Number of subjects analysed	130			
Units: percentage of subjects				
number (confidence interval 90%)	26.2 (18.8 to 34.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

End point title	Time to Disease Progression

End point description:

Time to progression (≥50% increase from the nadir in the individual sum of the products of the diameters of any index lesion; the reappearance of pathology, enlargement of liver/spleen, or unequivocal progression of non-measurable disease or appearance of any new lesions) was defined as the duration from the date of the first study drug dose to the date of relapse or progression as reported by the independent review committee and was determined using Kaplan-Meier product-limit estimates.

End point type	Secondary

End point timeframe:

Response was assessed after every 2 cycles of treatment and at completion of therapy, up until 30 September 2012 (data cutoff for analysis). Maximum duration on study was 1931 days.

End point values	Histopathologically-Confirmed Population			
Subject group type	Subject analysis set			
Number of subjects analysed	130			
Units: days				
median (confidence interval 95%)	182 (106 to 290)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Change in Eastern Cooperative Oncology Group (ECOG) Performance Status

End point description:

The ECOG scale is as follows: Grade 0: Fully active, able to perform all pre-disease activities without restriction; Grade 1: Restricted in physically strenuous activity, ambulatory, able to carry out light work; Grade 2: Ambulatory and capable of all self-care but unable to work. Up and about more than 50% of waking hours; Grade 3: Capable of only limited self-care, confined to bed or chair > 50% of waking hours; Grade 4: Completely disabled. Cannot carry on any self-care. Confined to bed or chair. Data reported is the shift from Baseline ECOG score to best on-study assessment score.

End point type	Secondary

End point timeframe:

From Baseline up until 30 September 2012 (data cutoff for analysis). Maximum duration on study was 1931 days.

End point values	Missing ECOG	Best ECOG = 0	Best ECOG = 1	Best ECOG = 2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5	40	57	19
Units: subjects				
Missing Baseline ECOG Score	1	0	0	0
Baseline ECOG Score = 0	2	26	16	1
Baseline ECOG Score = 1	1	13	35	12
Baseline ECOG Score = 2	1	1	6	6
Baseline ECOG Score = 3	0	0	0	0
Baseline ECOG Score = 4	0	0	0	0

End point values	Best ECOG = 3	Best ECOG = 4		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	4		
Units: subjects				
Missing Baseline ECOG Score	0	0		
Baseline ECOG Score = 0	0	1		
Baseline ECOG Score = 1	4	2		
Baseline ECOG Score = 2	2	1		
Baseline ECOG Score = 3	0	0		
Baseline ECOG Score = 4	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event or experience (AE) is defined as any untoward medical occurrence, which does not necessarily have to have a causal relationship with this treatment. A serious AE is any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is an important medical event or condition. Related AEs are defined as those considered by the Investigator to have a possible, probable, or very likely/certain relationship to the study drug. AEs were graded as mild (1), moderate (2), severe (3), life-threatening (4), or death (5). TEAEs occurred from the first dose of study medication through the end of the study (30 days post last dose) or any event that was present at baseline but worsened in intensity or was subsequently considered drug-related by the Investigator through end of study.

End point type	Secondary

End point timeframe:

From first dose of study treatment until the final study visit, which occurred 30 days after receiving the last dose. Mean duration of treatment up until 30 September 2012 (data cutoff for analysis) was 169 days.

End point values	Romidepsin			
Subject group type	Reporting group			
Number of subjects analysed	131			
Units: subjects				
TEAE	128			
≥ Grade 3 TEAE	89			
≥ Grade 4 TEAE	27			
Serious TEAE	61			
TEAE Leading to Discontinuation	25			
Deaths within 30 days of Last Dose	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported and documented throughout the study from first dose of study treatment until the final study visit, which occurred 30 days after receiving the last dose. The mean duration of treatment was 210 days.

Adverse event reporting additional description:

NOTE: events shown include data from 6 subjects who were ongoing in study treatment at the time of the last data cut-off (30-Sep-2012), which updated the mean duration of treatment from 196 to 210 days.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Romidepsin

Reporting group description:

Subjects received romidepsin 14 mg/m^2 administered intravenously over 4 hours on Days 1, 8, and 15 of a 28-day cycle. Subjects continued on monthly cycles of romidepsin.

Serious adverse events	Romidepsin		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 131 (47.33%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasm malignant			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour flare			

subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Deep vein thrombosis				
subjects affected / exposed	5 / 131 (3.82%)			
occurrences causally related to treatment / all	3 / 5			
deaths causally related to treatment / all	0 / 0			
Hypotension				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chest pain				
subjects affected / exposed	3 / 131 (2.29%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Chills				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Fatigue				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multi-organ failure				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Oedema peripheral				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	11 / 131 (8.40%)			
occurrences causally related to treatment / all	5 / 14			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Cytokine release syndrome				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	3 / 131 (2.29%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Hypoxia				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 131 (2.29%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Mental status changes				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Investigations				
Aspartate aminotransferase increased				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Aspiration tracheal				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
C-reactive protein increased				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram T wave inversion				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Electrocardiogram repolarisation abnormality				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatic enzyme increased				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Liver function test abnormal				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Cardiogenic shock				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subendocardial ischaemia				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Somnolence			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 131 (2.29%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Anaemia haemolytic autoimmune			
subjects affected / exposed	2 / 131 (1.53%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Febrile neutropenia				
subjects affected / exposed	4 / 131 (3.05%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	3 / 131 (2.29%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 131 (2.29%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Angle closure glaucoma				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	4 / 131 (3.05%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Colitis				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			

Diarrhoea				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastric ulcer				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intussusception				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower gastrointestinal haemorrhage				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Peritonitis				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	6 / 131 (4.58%)			
occurrences causally related to treatment / all	4 / 6			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Hydronephrosis				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvi-ureteric obstruction				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Proteinuria				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal failure				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Renal failure acute				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Urinary retention				

subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Periarthritis			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tendon disorder			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Candida sepsis			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Catheter related infection			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	5 / 131 (3.82%)		
occurrences causally related to treatment / all	3 / 11		
deaths causally related to treatment / all	0 / 0		

Erysipelas			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oral candidiasis			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumocystis jiroveci pneumonia			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	7 / 131 (5.34%)		
occurrences causally related to treatment / all	1 / 7		
deaths causally related to treatment / all	0 / 2		
Respiratory tract infection			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	6 / 131 (4.58%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	1 / 1		
Septic shock			

subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	2 / 131 (1.53%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	3 / 131 (2.29%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Failure to thrive				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 131 (0.76%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				

subjects affected / exposed	2 / 131 (1.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Magnesium deficiency			
subjects affected / exposed	1 / 131 (0.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	2 / 131 (1.53%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Romidepsin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	124 / 131 (94.66%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	10 / 131 (7.63%)		
occurrences (all)	13		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 131 (16.79%)		
occurrences (all)	42		
Chest pain			
subjects affected / exposed	8 / 131 (6.11%)		
occurrences (all)	14		
Chills			
subjects affected / exposed	14 / 131 (10.69%)		
occurrences (all)	22		
Fatigue			
subjects affected / exposed	53 / 131 (40.46%)		
occurrences (all)	120		
Oedema			

subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	7 / 131 (5.34%) 10 13 / 131 (9.92%) 23 10 / 131 (7.63%) 12 44 / 131 (33.59%) 75		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 24 / 131 (18.32%) 36 16 / 131 (12.21%) 21 8 / 131 (6.11%) 11 8 / 131 (6.11%) 8		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 9 / 131 (6.87%) 9 9 / 131 (6.87%) 9		
Investigations Weight decreased subjects affected / exposed occurrences (all)	 14 / 131 (10.69%) 15		
Cardiac disorders			

Tachycardia			
subjects affected / exposed	13 / 131 (9.92%)		
occurrences (all)	17		
Nervous system disorders			
Dizziness			
subjects affected / exposed	10 / 131 (7.63%)		
occurrences (all)	27		
Dysgeusia			
subjects affected / exposed	27 / 131 (20.61%)		
occurrences (all)	39		
Headache			
subjects affected / exposed	19 / 131 (14.50%)		
occurrences (all)	35		
Lethargy			
subjects affected / exposed	8 / 131 (6.11%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 131 (24.43%)		
occurrences (all)	84		
Leukopenia			
subjects affected / exposed	15 / 131 (11.45%)		
occurrences (all)	28		
Neutropenia			
subjects affected / exposed	37 / 131 (28.24%)		
occurrences (all)	90		
Thrombocytopenia			
subjects affected / exposed	53 / 131 (40.46%)		
occurrences (all)	181		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	15 / 131 (11.45%)		
occurrences (all)	24		
Abdominal pain upper			
subjects affected / exposed	9 / 131 (6.87%)		
occurrences (all)	11		
Constipation			

subjects affected / exposed occurrences (all)	39 / 131 (29.77%) 65		
Diarrhoea subjects affected / exposed occurrences (all)	46 / 131 (35.11%) 84		
Dyspepsia subjects affected / exposed occurrences (all)	12 / 131 (9.16%) 14		
Nausea subjects affected / exposed occurrences (all)	76 / 131 (58.02%) 246		
Stomatitis subjects affected / exposed occurrences (all)	14 / 131 (10.69%) 36		
Vomiting subjects affected / exposed occurrences (all)	48 / 131 (36.64%) 127		
Skin and subcutaneous tissue disorders Dry skin subjects affected / exposed occurrences (all)	8 / 131 (6.11%) 8		
Night sweats subjects affected / exposed occurrences (all)	9 / 131 (6.87%) 9		
Pruritus subjects affected / exposed occurrences (all)	12 / 131 (9.16%) 13		
Rash subjects affected / exposed occurrences (all)	11 / 131 (8.40%) 14		
Skin lesion subjects affected / exposed occurrences (all)	11 / 131 (8.40%) 11		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	7 / 131 (5.34%)		
occurrences (all)	10		
Back pain			
subjects affected / exposed	9 / 131 (6.87%)		
occurrences (all)	13		
Muscle spasms			
subjects affected / exposed	12 / 131 (9.16%)		
occurrences (all)	14		
Myalgia			
subjects affected / exposed	8 / 131 (6.11%)		
occurrences (all)	34		
Pain in extremity			
subjects affected / exposed	7 / 131 (5.34%)		
occurrences (all)	8		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	7 / 131 (5.34%)		
occurrences (all)	10		
Oral candidiasis			
subjects affected / exposed	7 / 131 (5.34%)		
occurrences (all)	8		
Upper respiratory tract infection			
subjects affected / exposed	12 / 131 (9.16%)		
occurrences (all)	19		
Urinary tract infection			
subjects affected / exposed	7 / 131 (5.34%)		
occurrences (all)	9		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	38 / 131 (29.01%)		
occurrences (all)	54		
Decreased appetite			
subjects affected / exposed	12 / 131 (9.16%)		
occurrences (all)	16		
Hypokalaemia			

subjects affected / exposed	14 / 131 (10.69%)		
occurrences (all)	17		
Hypomagnesaemia			
subjects affected / exposed	9 / 131 (6.87%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 September 2011	Amendment provided for a reduced treatment and disease assessment schedule for patients on long-term therapy. Specifically, patients who continued maintenance dosing beyond Cycle 12 were to receive at least 2 doses per cycle through at least Cycle 24 and must have remained at this regimen for a minimum of 6 months prior to reduction to 1 dose per cycle. For patients who remained on study for more than 36 months (3 years), disease assessments could be reduced from every 2 cycles to every 4 cycles. For all patients, disease assessments were to be conducted at the time of study discontinuation or whenever progression of disease was suspected by clinical findings.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported