



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, jejjones@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/m² 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 Specified | 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/m² 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/m² 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$ 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 $\geq 50\%$.

| | |
|----------------|-----------|
| 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 ($\geq 50\%$ 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/m² 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 | | | |

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

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

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