



Clinical trial results:

“Randomized, Multicenter, Open-label, Phase III Study of Plitidepsin in Combination with Dexamethasone vs. Dexamethasone Alone in Patients with Relapsed/Refractory Multiple Myeloma”.

Summary

| | |
|--------------------------|--|
| EudraCT number | 2009-016138-29 |
| Trial protocol | FR GB ES AT NL DE BE CZ IT GR IE PT PL |
| Global end of trial date | 20 November 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 18 November 2018 |
| First version publication date | 18 November 2018 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | APL-C-001-09 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01102426 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pharma Mar, S.A. |
| Sponsor organisation address | Avenida de los Reyes, 1 Polígono Industrial "La Mina", Colmenar Viejo, Madrid, Spain, 28770 |
| Public contact | Clinical Development, Department of PharmaMar's Oncology., Business Unit., Pharmamar, S.A. , 34 918466000, clinicaltrials@pharmamar.com |
| Scientific contact | Clinical Development, Department of PharmaMar's Oncology., Business Unit., Pharmamar, S.A., 34 918466000, clinicaltrials@pharmamar.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 | 08 October 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 November 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of plitidepsin in combination with dexamethasone vs. dexamethasone alone as measured by progression-free survival (PFS) in patients with relapsed/refractory multiple myeloma (MM).

Protection of trial subjects:

The study was in compliance with ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

All the patients have to receive DXM with or without Plitidepsin.

The administration of each study medication was as follows:

Arm A:

- DXM: 40 mg orally on Day 1, 8, 15 and 22 every four weeks (q4wk) at least one hour before plitidepsin infusion.
- Plitidepsin: 5 mg/m² i.v. diluted to a total volume of 250 mL in 0.9% saline (or 5% glucose) via a central venous catheter (suggested) or diluted to a total volume of 500 mL in 0.9% saline (or 5% glucose) via a peripheral line.

Infusion was performed through a pump device over three hours (fixed rate) on Day 1 and 15 q4wk.

Arm B:

- DXM: 40 mg orally on Day 1, 8, 15 and 22 q4wk.

A cycle was defined as a four-week period

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 29 June 2010 |
| 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 | Netherlands: 9 |
| Country: Number of subjects enrolled | Poland: 4 |
| Country: Number of subjects enrolled | Portugal: 3 |
| Country: Number of subjects enrolled | Spain: 20 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Austria: 28 |
| Country: Number of subjects enrolled | Belgium: 15 |
| Country: Number of subjects enrolled | Czech Republic: 33 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 9 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Greece: 19 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Korea, Republic of: 12 |
| Country: Number of subjects enrolled | New Zealand: 8 |
| Country: Number of subjects enrolled | Australia: 37 |
| Country: Number of subjects enrolled | United States: 7 |
| Country: Number of subjects enrolled | Taiwan: 12 |
| Worldwide total number of subjects | 255 |
| EEA total number of subjects | 179 |

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) | 124 |
| From 65 to 84 years | 129 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

A total of 255 patients were enrolled. 171 Group A (Plitidepsin in combination with DXM) and 84 Group B (DXM alone).

Enrolled patients between 29Jun10 and 19May15 (Last randomization). The first dose of the first patient was given on 19May15 and the last dose of the last patient was given on 07Aug17.

Pre-assignment

Screening details:

IC Signed, Age ≥ 18 , ECOG PS ≤ 2 , Life expectancy ≥ 3 mo, Previously diagnosed MM, Relapsed or relapsed and refractory MM between 3&6, Previous bortezomib-containing and lenalidomide containing regimens, Measurable disease, At least 2week washout period since end last therapy, Adequate BM, renal, hepatic&metabolic, Normal LVEF by ECHO/MUGA, negative pregnancy test

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

Not applicable

Arms

| | |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A (plitidepsin plus DXM) |

Arm description:

Arm A (plitidepsin plus DXM)

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Aplidin |
| Investigational medicinal product code | |
| Other name | Plitidepsin |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

5 mg/m² i.v. diluted to a total volume of 250 mL in 0.9% saline (or 5% glucose) via a central venous catheter (suggested) or diluted to a total volume of 500 mL in 0.9% saline (or 5% glucose) via a peripheral line.

Infusion was performed through a pump device over three hours (fixed rate) on Day 1 and 15 q4wk.

| | |
|--|---------------|
| Investigational medicinal product name | DXM |
| Investigational medicinal product code | Dexamethasone |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

40 mg orally on Day 1, 8, 15 and 22 every four weeks (q4wk) at least one hour before plitidepsin infusion.

| | |
|-------------------|-------------------|
| Arm title | Arm B (DXM alone) |
| Arm description: | |
| Arm B (DXM alone) | |
| Arm type | Active comparator |

| | |
|--|---------------|
| Investigational medicinal product name | DXM |
| Investigational medicinal product code | Dexamethasone |
| Other name | |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

DXM: 40 mg orally on Day 1, 8, 15 and 22 q4wk.

| Number of subjects in period 1 | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) |
|---------------------------------------|------------------------------|-------------------|
| Started | 171 | 84 |
| Completed | 0 | 0 |
| Not completed | 171 | 84 |
| Physician decision | 7 | 4 |
| Consent withdrawn by subject | 24 | 6 |
| Toxicity | 15 | 3 |
| Randomized but not treated | 4 | 1 |
| Death | 20 | 5 |
| Other | 22 | 10 |
| Progressive Disease | 79 | 18 |
| Transferred to other arm/group | - | 37 |

Baseline characteristics

Reporting groups

| | |
|--|------------------------------|
| Reporting group title | Arm A (plitidepsin plus DXM) |
| Reporting group description: Arm A (plitidepsin plus DXM) | |
| Reporting group title | Arm B (DXM alone) |
| Reporting group description: Arm B (DXM alone) | |

| Reporting group values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | Total |
|---------------------------------|------------------------------|-------------------|-------|
| Number of subjects | 171 | 84 | 255 |
| Age categorical | | | |
| Years | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 88 | 36 | 124 |
| From 65-84 years | 82 | 47 | 129 |
| 85 years and over | 1 | 1 | 2 |
| Age continuous | | | |
| Units: years | | | |
| median | 64.0 | 65.0 | |
| full range (min-max) | 36 to 85 | 42 to 85 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 74 | 49 | 123 |
| Male | 97 | 35 | 132 |
| ECOG PS | | | |
| PS Performance status | | | |
| Units: Subjects | | | |
| PS 0 | 68 | 31 | 99 |
| PS 1 | 74 | 42 | 116 |
| PS 2 | 28 | 11 | 39 |
| PS 3 | 1 | 0 | 1 |
| MM type at diagnosis | | | |
| Units: Subjects | | | |
| Non Secretory | 6 | 1 | 7 |
| Secretory IgA | 35 | 21 | 56 |
| Secretory IgD | 1 | 1 | 2 |
| Secretory IgG | 101 | 51 | 152 |
| Secretory IgM | 1 | 0 | 1 |
| Secretory Light chain disease | 27 | 10 | 37 |
| Durie-Salmon stage at diagnosis | | | |
| Units: Subjects | | | |
| Stage A | 0 | 1 | 1 |
| Stage IA | 21 | 9 | 30 |
| Stage IB | 0 | 2 | 2 |
| Stage II | 3 | 1 | 4 |
| Stage IIA | 44 | 20 | 64 |

| | | | |
|---|---------------|---------------|-----|
| Stage IIB | 1 | 0 | 1 |
| Stage III | 2 | 1 | 3 |
| Stage IIIA | 85 | 43 | 128 |
| Stage IIIB | 14 | 7 | 21 |
| Not Durie-Salmon stage at diagnosis | 1 | 0 | 1 |
| ISS stage at diagnosis | | | |
| Units: Subjects | | | |
| Stage I | 72 | 33 | 105 |
| Stage II | 41 | 18 | 59 |
| Stage III | 23 | 15 | 38 |
| Not ISS stage at diagnosis | 35 | 18 | 53 |
| Cytogenetic risk group at diagnosis | | | |
| NA: not available; ND: not done; UK: unknown. | | | |
| Units: Subjects | | | |
| Standard risk | 34 | 21 | 55 |
| High risk | 38 | 16 | 54 |
| NA/ND/UK | 99 | 47 | 146 |
| Prior radiotherapy | | | |
| Units: Subjects | | | |
| Yes | 68 | 35 | 103 |
| No | 103 | 49 | 152 |
| Hb | | | |
| Units: g/dL | | | |
| median | 10.4 | 10.1 | |
| full range (min-max) | 7.0 to 14.6 | 7.4 to 14.6 | - |
| Platelets | | | |
| Units: 10 ⁹ /L | | | |
| median | 140 | 154 | |
| full range (min-max) | 11.0 to 517.0 | 24.0 to 452.0 | - |
| CrCL | | | |
| creatinine clearance | | | |
| Units: mL/min | | | |
| median | 72.9 | 69.4 | |
| full range (min-max) | 21.9 to 252.2 | 23.0 to 137.0 | - |
| Time from first diagnosis to randomization | | | |
| Units: months | | | |
| median | 71.8 | 70.0 | |
| full range (min-max) | 0.1 to 277.2 | 19.5 to 178.9 | - |
| Time from last PD/relapse to first study dose | | | |
| PD, Progressive disease | | | |
| Units: weeks | | | |
| median | 6.1 | 6.4 | |
| full range (min-max) | -0.4 to 83.1 | 1.0 to 101.7 | - |
| Beta-2 microglobulin | | | |
| Units: mg/L | | | |
| median | 4.1 | 4.2 | |
| full range (min-max) | 0.0 to 27.3 | 0.2 to 65.0 | - |
| Number of lines of prior systemic therapy | | | |

| | | | |
|----------------------|--------|--------|---|
| Units: Lines | | | |
| median | 4 | 4 | |
| full range (min-max) | 2 to 6 | 3 to 7 | - |

End points

End points reporting groups

| | |
|------------------------------|------------------------------|
| Reporting group title | Arm A (plitidepsin plus DXM) |
| Reporting group description: | |
| Arm A (plitidepsin plus DXM) | |
| Reporting group title | Arm B (DXM alone) |
| Reporting group description: | |
| Arm B (DXM alone) | |

Primary: Progression-free Survival (Independent Review Committee)

| | |
|--|--|
| End point title | Progression-free Survival (Independent Review Committee) |
| End point description: | |
| <p>The primary study analysis was based on externally assessed PFS data (An external IRC, blinded to treatment arm, assigned a progression or censoring date for each patient based on laboratory data and radiological and bone marrow assessments when required, and evaluation of all relevant clinical information, according to a predefined algorithm) in the ITT efficacy population, defined as all patients randomized to either treatment arm. PFS was calculated from randomization to the first evidence of PD (IMWG criteria) or death due to any cause.</p> <p>If the patient received further antitumor therapy before PD, PFS was censored on the date of the last disease assessment prior to the administration.</p> <p>If the patient was lost to follow-up , the PFS was censored at the date of last valid tumor assessment before the missing evaluations.</p> <p>Event was assigned as the first time a PD is reported without the necessity of its confirmation.</p> | |
| End point type | Primary |
| End point timeframe: | |
| Overall period - IRC-All Randomized Patients | |

| End point values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | | |
|----------------------------------|------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 84 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.6 (1.9 to 3.0) | 1.7 (1.1 to 2.0) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Arm A compared to Arm B |
| Comparison groups | Arm B (DXM alone) v Arm A (plitidepsin plus DXM) |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.0054 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.65 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.477 |
| upper limit | 0.885 |

Notes:

[1] - PFS at 6 months (95% CI): Arm A: 20.0% (13.1-26.9%) vs Arm B: 10.0% (2.0-18.0%); p=0.0618

[2] - Cox regression: HR p=0.0062

Secondary: Progression-free Survival (Investigator assessment)

| | |
|-----------------|---|
| End point title | Progression-free Survival (Investigator assessment) |
|-----------------|---|

End point description:

The secondary study analysis was based on Investigator's assessment PFS data in the ITT efficacy population, defined as all patients randomized to either treatment arm. PFS was calculated from randomization to the first evidence of PD (IMWG criteria) or death due to any cause. If the patient received further antitumor therapy before PD and within the timeframe expected for first follow-up, PFS was censored on the date of the last disease assessment prior to the administration of this antitumor therapy. If the patient was lost to follow-up for the assessment of progression, or had more than one missing follow-up between the date of last tumor assessment and the date of progression, death or further antitumor therapy, the PFS was censored at the date of last valid tumor assessment before the missing evaluations. Event was assigned as the first time a PD is reported without the necessity of its confirmation.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Overall period - IA - All Randomized Patients

| End point values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | | |
|----------------------------------|------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 84 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.9 (2.1 to 3.7) | 1.1 (1.0 to 1.9) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Arm A compared to Arm B |
| Comparison groups | Arm A (plitidepsin plus DXM) v Arm B (DXM alone) |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | < 0.0001 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.512 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.382 |
| upper limit | 0.686 |

Notes:

[3] - PFS at 6 months (95% CI): Arm A: 26.4% (19.1-33.7%) vs Arm B: 8.1% (1.9-14.3%); p=0.0002

[4] - Cox regression HR: p<0.0001

Secondary: Best Overall Response (Independent Review Committee)

| | |
|--|--|
| End point title | Best Overall Response (Independent Review Committee) |
| End point description: | |
| CR; complete response; DXM, dexamethasone; MR; minor response; NE, not evaluable; ORR, overall response rate; P, plitidepsin; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD; stable disease; VGPR, very good partial response. | |
| End point type | Secondary |
| End point timeframe: | |
| Overall period | |

| End point values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | | |
|-----------------------------|------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 84 | | |
| Units: subjects | | | | |
| VGPR | 2 | 0 | | |
| PR | 15 | 1 | | |
| MR | 22 | 2 | | |
| SD | 43 | 21 | | |
| PD | 41 | 35 | | |
| NE | 48 | 25 | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Overall response rate |
| Comparison groups | Arm A (plitidepsin plus DXM) v Arm B (DXM alone) |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | < 0.0001 |
| Method | Fisher exact |

Notes:

[5] - ORR (95% CI): Arm A: 22.8% (16.8-29.8%) vs Arm B: 3.6% (0.7-10.1%); p<0.0001
 ORR (excluding MR) (95% CI): Arm A: 9.9% (5.9-15.4%) vs Arm B: 1.2% (0.03-6.5%); p=0.0085

Secondary: Duration of Response (Independent Review Committee)

| | |
|-----------------|---|
| End point title | Duration of Response (Independent Review Committee) |
|-----------------|---|

End point description:

DR was calculated from the date of first documentation of response to the date of disease progression or death. The same censoring rules described above for PFS calculation were also considered for DR.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Overall period - IRC- All Responder Patients

| End point values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | | |
|----------------------------------|------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 39 ^[6] | 3 ^[7] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.7 (2.7 to 10.5) | 1.8 (1.8 to 5.5) | | |

Notes:

[6] - Responder Patients

[7] - Responder Patients

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Arm A compared to Arm B |
| Comparison groups | Arm A (plitidepsin plus DXM) v Arm B (DXM alone) |
| Number of subjects included in analysis | 42 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | = 0.1015 ^[9] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.384 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.113 |
| upper limit | 1.303 |

Notes:

[8] - DR at 6 months (95% CI): Arm A: 41.2% (24.6-57.7%) vs 0.0% (0.0-.%)

[9] - Cox regression HR: 0.1247

Secondary: Overall survival

| | |
|--|------------------|
| End point title | Overall survival |
| End point description: | |
| OS was defined as the time from the date of randomization to the date of death or last contact | |
| End point type | Secondary |
| End point timeframe: | |
| Overall period - All Randomized Patients | |

| End point values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | | |
|----------------------------------|------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 84 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 11.6 (9.2 to 16.1) | 8.9 (6.0 to 15.4) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Arm A compared to Arm B |
| Comparison groups | Arm A (plitidepsin plus DXM) v Arm B (DXM alone) |
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.1261 ^[11] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.797 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.596 |
| upper limit | 1.067 |

Notes:

[10] - OS at 12 months (95% CI): Arm A: 48.3% (40.4-56.2%) vs Arm B: 42.1% (31.3-52.9%); p=0.3625

OS at 24 months (95% CI): Arm A: 30.8% (23.3-38.3%) vs Arm B: 21.0% (12.0-30.1%); p=0.1037

[11] - Cox regression HR: p=0.1273

Secondary: Best Overall Response (Investigator assessment)

| | |
|---|---|
| End point title | Best Overall Response (Investigator assessment) |
| End point description: | |
| CR; complete response; DXM, dexamethasone; MR; minor response; NE, not evaluable; ORR, overall response rate; P, plitidepsin; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD; stable disease; VGPR, very good partial resp | |
| End point type | Secondary |
| End point timeframe: | |
| Overall period | |

| End point values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | | |
|-----------------------------|------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 171 | 84 | | |
| Units: subjects | | | | |
| VGPR | 4 | 0 | | |
| PR | 16 | 1 | | |
| MR | 31 | 0 | | |
| SD | 61 | 31 | | |
| PD | 37 | 39 | | |
| NE | 22 | 13 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Overall response rate |
| Comparison groups | Arm A (plitidepsin plus DXM) v Arm B (DXM alone) |
| Number of subjects included in analysis | 255 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[12] |
| P-value | < 0.0001 |
| Method | Fisher exact |

Notes:

[12] - ORR (95% CI): Arm A: 29.8% (23.1-37.3%) vs Arm B: 1.2% (0.03-6.5%); p<0.0001

ORR (excluding MR) (95% CI): Arm A: 11.7% (7.3-17.5%) vs Arm B: 1.2% (0.03-6.5%); p=0.0029

Secondary: Duration of Response (Investigator assessment)

| | |
|---|--|
| End point title | Duration of Response (Investigator assessment) |
| End point description: | |
| DR was calculated from the date of first documentation of response to the date of disease progression or death. The same censoring rules described above for PFS calculation were also considered for DR. | |
| End point type | Secondary |
| End point timeframe: | |
| Overall period | |

| End point values | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | | |
|----------------------------------|------------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 ^[13] | 1 ^[14] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.1 (3.2 to 6.2) | 0.9 (-999 to 999) | | |

Notes:

[13] - Responder Patients

[14] - Responder Patients

-999,999 = Interval could not be calculated

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Arm A compared to Arm B |
| Comparison groups | Arm B (DXM alone) v Arm A (plitidepsin plus DXM) |
| Number of subjects included in analysis | 52 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[15] |
| P-value | = 0.0001 ^[16] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.043 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.004 |
| upper limit | 0.479 |

Notes:

[15] - DR at 6 months (95% CI): Arm A: 38.2% (23.7-52.8%) vs 0.0% (0.0-.%)

[16] - Cox regression HR: 0.0105

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | Arm A (plitidepsin plus DXM) |
|-----------------------|------------------------------|

Reporting group description:

Arm A (plitidepsin plus DXM)

| | |
|-----------------------|-------------------|
| Reporting group title | Arm B (DXM alone) |
|-----------------------|-------------------|

Reporting group description:

Arm B (DXM alone)

| Serious adverse events | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | |
|---|------------------------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 99 / 167 (59.28%) | 26 / 83 (31.33%) | |
| number of deaths (all causes) | 126 | 74 | |
| number of deaths resulting from adverse events | 23 | 5 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Oesophageal squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasmablastic lymphoma | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |

| | | | |
|--|-----------------|----------------|--|
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subclavian vein thrombosis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis superficial | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 4 / 167 (2.40%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 167 (4.79%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden death | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 167 (1.20%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrothorax | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurisy | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Productive cough | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung disorder | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 7 / 167 (4.19%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 10 / 10 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 12 / 12 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Blood creatine phosphokinase MB increased | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 8 / 9 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic enzyme abnormal | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Troponin I increased | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cells increased | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Injury, poisoning and procedural complications | | | |
| Drug administration error | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transfusion reaction | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|----------------|--|
| Upper limb fracture | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 3 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systolic dysfunction | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraplegia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paresis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Quadriparesis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetic neuropathy | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 3 / 83 (3.61%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperviscosity syndrome | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticular perforation | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal ulcer | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enteritis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 4 / 167 (2.40%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 3 / 8 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 4 / 167 (2.40%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 3 / 83 (3.61%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Calculus urinary | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure chronic | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mobility decreased | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myopathy | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Myopathy toxic | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myositis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteolysis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Atypical pneumonia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis infectious | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung infection | | | |

| | | | |
|---|------------------|----------------|--|
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jiroveci pneumonia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 15 / 167 (8.98%) | 3 / 83 (3.61%) | |
| occurrences causally related to treatment / all | 9 / 18 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 1 | |
| Pneumonia fungal | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pseudomonal bacteraemia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 3 / 167 (1.80%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Sepsis | | | |
| subjects affected / exposed | 9 / 167 (5.39%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 3 / 9 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 4 / 167 (2.40%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 167 (2.40%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium colitis | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary tuberculosis | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 1 / 83 (1.20%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fluid overload | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 2 / 83 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 4 / 167 (2.40%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Arm A (plitidepsin plus DXM) | Arm B (DXM alone) | |
|---|------------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 161 / 167 (96.41%) | 80 / 83 (96.39%) | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 22 / 167 (13.17%) | 0 / 83 (0.00%) | |
| occurrences (all) | 48 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 11 / 167 (6.59%) | 0 / 83 (0.00%) | |
| occurrences (all) | 20 | 0 | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 28 / 167 (16.77%) | 0 / 83 (0.00%) | |
| occurrences (all) | 41 | 0 | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 15 / 167 (8.98%) | 1 / 83 (1.20%) | |
| occurrences (all) | 34 | 1 | |
| Weight decreased | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 1 / 83 (1.20%) | |
| occurrences (all) | 13 | 1 | |
| Platelet count decreased | | | |

| | | | |
|---|-----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 167 (4.19%) 67 | 5 / 83 (6.02%) 21 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 14 / 167 (8.38%) | 5 / 83 (6.02%) | |
| occurrences (all) | 17 | 6 | |
| Hypotension | | | |
| subjects affected / exposed | 16 / 167 (9.58%) | 1 / 83 (1.20%) | |
| occurrences (all) | 17 | 1 | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 18 / 167 (10.78%) | 5 / 83 (6.02%) | |
| occurrences (all) | 18 | 6 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 69 / 167 (41.32%) | 34 / 83 (40.96%) | |
| occurrences (all) | 203 | 97 | |
| Neutropenia | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 2 / 83 (2.41%) | |
| occurrences (all) | 26 | 3 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 15 / 167 (8.98%) | 8 / 83 (9.64%) | |
| occurrences (all) | 47 | 15 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 32 / 167 (19.16%) | 9 / 83 (10.84%) | |
| occurrences (all) | 60 | 11 | |
| Chest pain | | | |
| subjects affected / exposed | 9 / 167 (5.39%) | 2 / 83 (2.41%) | |
| occurrences (all) | 12 | 2 | |
| Fatigue | | | |
| subjects affected / exposed | 55 / 167 (32.93%) | 18 / 83 (21.69%) | |
| occurrences (all) | 95 | 22 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 31 / 167 (18.56%) | 5 / 83 (6.02%) | |
| occurrences (all) | 45 | 6 | |

| | | | |
|--|--------------------------|------------------------|--|
| Pyrexia subjects affected / exposed occurrences (all) | 32 / 167 (19.16%) 50 | 11 / 83 (13.25%) 14 | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 16 / 167 (9.58%) 16 | 1 / 83 (1.20%) 1 | |
| Constipation subjects affected / exposed occurrences (all) | 21 / 167 (12.57%) 23 | 5 / 83 (6.02%) 7 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 57 / 167 (34.13%) 80 | 8 / 83 (9.64%) 10 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 9 / 167 (5.39%) 12 | 4 / 83 (4.82%) 5 | |
| Nausea subjects affected / exposed occurrences (all) | 76 / 167 (45.51%) 122 | 17 / 83 (20.48%) 19 | |
| Vomiting subjects affected / exposed occurrences (all) | 41 / 167 (24.55%) 57 | 3 / 83 (3.61%) 3 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 31 / 167 (18.56%) 42 | 9 / 83 (10.84%) 10 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 23 / 167 (13.77%) 36 | 3 / 83 (3.61%) 3 | |
| Epistaxis subjects affected / exposed occurrences (all) | 10 / 167 (5.99%) 11 | 6 / 83 (7.23%) 8 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 18 / 167 (10.78%) 23 | 10 / 83 (12.05%) 11 | |

| | | | |
|---|-------------------|------------------|--|
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 167 (4.79%) | 6 / 83 (7.23%) | |
| occurrences (all) | 8 | 6 | |
| Back pain | | | |
| subjects affected / exposed | 16 / 167 (9.58%) | 15 / 83 (18.07%) | |
| occurrences (all) | 18 | 22 | |
| Bone pain | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 15 / 83 (18.07%) | |
| occurrences (all) | 13 | 17 | |
| Muscular weakness | | | |
| subjects affected / exposed | 21 / 167 (12.57%) | 3 / 83 (3.61%) | |
| occurrences (all) | 27 | 5 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 1 / 83 (1.20%) | |
| occurrences (all) | 14 | 1 | |
| Myalgia | | | |
| subjects affected / exposed | 30 / 167 (17.96%) | 3 / 83 (3.61%) | |
| occurrences (all) | 47 | 3 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 167 (2.99%) | 5 / 83 (6.02%) | |
| occurrences (all) | 5 | 5 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 14 / 167 (8.38%) | 5 / 83 (6.02%) | |
| occurrences (all) | 19 | 5 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 2 / 83 (2.41%) | |
| occurrences (all) | 13 | 2 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 34 / 167 (20.36%) | 5 / 83 (6.02%) | |
| occurrences (all) | 40 | 5 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 8 / 167 (4.79%) | 7 / 83 (8.43%) | |
| occurrences (all) | 9 | 11 | |

| | | | |
|-----------------------------|-------------------|----------------|--|
| Hyperglycaemia | | | |
| subjects affected / exposed | 11 / 167 (6.59%) | 3 / 83 (3.61%) | |
| occurrences (all) | 16 | 3 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 19 / 167 (11.38%) | 5 / 83 (6.02%) | |
| occurrences (all) | 23 | 5 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 28 December 2010 | <p>This protocol amendment included the following changes:</p> <ul style="list-style-type: none">-A retrospective analysis performed in all adult patients treated with single-agent plitidepsin in phase I (at the recommended dose) and phase II clinical trials showed plitidepsin administration through a peripheral vein safe enough to be considered in this q3wk schedule whenever a central venous line was deemed unsuitable for any reason (e.g., coagulation problems, technical difficulties, patient's refusal, etc.). Therefore, central venous catheter administration was suggested, but peripheral lines were also accepted.-The exact binomial 95% CI for RR was provided to clarify futility analysis rules, as requested by the IDMC.-Patient eligibility criteria were modified to allow inclusion of patients with stable atrial fibrillation, or patients with controlled infection on antibiotics.-Some assessment and procedures were modified:<ol style="list-style-type: none">1 To allow determination of direct bilirubin only if total bilirubin was above ULN.2 To extend from 14 to 28 days the timeframe for some baseline disease evaluation assessments (bone marrow, serum and urinary protein determinations, and radiological assessment in case of plasmacytomas); to clarify X-ray as the myeloma skeletal evaluation method;3 Following a request by the French Health Authorities as to be consistent with the information reported in the Investigator's Brochure of plitidepsin regarding coagulation tests monitoring, the sentence "close monitoring of patients taking oral anticoagulants is required" was added into the footnotes of the "Schedule of Assessments and Procedures" table and to the section "Concomitant Medication".4 Corrected in this amendment: IVRS system was used always in this trial, but due to a mistake during writing, v 1.0 of the protocol referred in the Patient Registration Section to a manual model (fast fact sheet).-A clarification regarding the extraction of PK blood samples was made. |

| | |
|---------------|---|
| 12 April 2013 | <p>This protocol amendment included the following changes:</p> <ul style="list-style-type: none"> -An update of study contact details and study timelines. -The implementation of the determination of direct bilirubin only if total bilirubin was above the ULN. -An update of the instructions for the preparation (dilution) of plitidepsin, in order to make them consistent with the preparation guidelines and other related documents that allow dilution with 5% glucose. -The removal of the need for assessing the creatinine clearance (measured) at baseline and end of treatment, leaving just the calculated creatinine clearance included in Biochemistry A. -To allow skeletal evaluation at baseline and end of treatment or whenever required, by X-ray or CT-scan, as long as the same procedure is used throughout the study. -To allow phone contacts for patients during survival follow-up whenever the patient's disease was so serious that he/she was unable to attend the clinic. This only applied to patients who were followed up after discontinuing treatment due to PD. -The conduct of the QTc substudy to assess the potential effects of plitidepsin on the heart activity of patients enrolled in this clinical trial. In particular the QTc interval, based on electrocardiogram evaluation, was to be recorded and studied. -An update of the PK section of the protocol. -An update of the Safety section in accordance with current regulations. -An update of the telephone number used for reporting SAEs to the PV Service out of office hours. -The IMWG uniform criteria for MM were initially used to document disease progression or response to treatment. In the second study stage, this protocol amendment implemented the use of the updated IMWG criteria only, and to remove the Durie et al. IMWG version shown in App. 5. Therefore, the decision taken at that time was to not confirm PD in two assessments. Due to this reason, the analysis of the primary endpoint was to identify the first PD reported with no further confirmation |
|---------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|------------------|--|------------------|
| 09 December 2012 | <p>An early futility analysis was performed when information from 40 patients in Arm A were evaluable for response. A response rate (IMWG criteria) of at least 30% (12 or more responses by IRC review) was taken as threshold for continuation of the study. A minimum response rate of 30% was considered as clinically significant in this setting. This result ensured that the lower limit of the exact binomial 95% CI for RR would be greater than 15% (95% CI in case of 12 responses would be 16.6%-46.5%).</p> <p>However, the information from all randomized patients in both arms at that time was used by the IDMC to evaluate the safety profile and to provide the Sponsor with a recommendation for the further study conduct. No claim for superiority in efficacy was to be formulated in this interim analysis and no alpha-spending for the analysis of PFS was foreseen. Accrual was to be on-hold while data for the futility analysis was assessed.</p> <p>For futility analysis based on objective RR, the All Evaluable Patients analysis dataset was used. On 9 December 2012, the evaluation by the IDMC of efficacy and safety data from the first 60 evaluable patients included in this study resulted in the recommendation to continue the trial unmodified, as the study met the established efficacy threshold of 30% response rate according to IMWG criteria pre-specified in the protocol (RR in Arm A, plitidepsin plus DXM, was 37.8%). No safety issues were reported. Therefore, patient accrual was resumed.</p> | 09 December 2012 |
|------------------|--|------------------|

Notes:

Limitations and caveats

None reported