



Clinical trial results: Phase II Dose Optimization, Open-Label Clinical Trial of Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2009-016054-40 |
| Trial protocol | ES |
| Global end of trial date | 30 July 2013 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 29 July 2016 |
| First version publication date | 29 July 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | PM104-B-002-09 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Pharma Mar, S.A. |
| Sponsor organisation address | Avda de los Reyes, 1, Polígono Industrial La Mina, Colmenar Viejo, Madrid, Spain, 28770 |
| Public contact | Clinical Development Department of PharmaMar's Oncology, Business Unit., Pharma Mar, S.A., +34 918466000, clinicaltrials@pharmamar.com |
| Scientific contact | Clinical Development Department of PharmaMar's Oncology, Business Unit., Pharma Mar, 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 | 01 December 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 12 April 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 July 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Dose optimization phase:

Primary objective:

To determine the recommended dose (RD) for PM00104 administered as 1-hour (h) intravenous (i.v.) infusion on Days (D) 1, 8 and 15 every four weeks (q4wk) in relapsed/refractory multiple myeloma (MM) patients

Dose expansion phase:

Primary objective:

To analyze the efficacy following treatment with PM00104 in patients with MM relapsed or refractory to standard therapy at the RD established during the dose optimization phase.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 08 March 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------|
| Country: Number of subjects enrolled | Spain: 36 |
| Worldwide total number of subjects | 36 |
| EEA total number of subjects | 36 |

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) | 24 |
| From 65 to 84 years | 12 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

From 8 March 2010 to 12 December 2012 in ten sites in Spain

Pre-assignment

Screening details:

Patients had to give written informed consent, Age \geq 18 years, previously diagnosed with MM, have relapsed or relapsed/refractory disease, have measurable disease, recovery from any toxicity derived from previous treatments, have some adequate laboratory values, performance status \leq 2, Life expectancy \geq 3 months, LVEF of at least 50%.

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Dose optimization phase |

Arm description:

Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. A dose optimization phase was conducted to determine the appropriate dose of PM00104 in relapsed/refractory MM patients

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Zalypsis® |
| Investigational medicinal product code | PM00104 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A treatment cycle consisted of the administration of three i.v. 1-h infusions of PM00104 on D1, D8 and D15. Treatment cycles were to be repeated every four weeks. PM00104 administration through a central catheter and by specialized on-site study personnel was mandatory. PM00104 was provided as a powder for concentrate for solution for infusion in only one strength of 2.5 mg per vial.

| | |
|------------------|----------------------|
| Arm title | Dose expansion phase |
|------------------|----------------------|

Arm description:

Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. Once the recommended dosage had been defined, up to 37 more patients were to be recruited into the dose expansion phase in order to evaluate the anti-MM effects of PM00104. These patients were to receive single-agent PM00104 at the RD established in the earlier dose optimization phase, given as 1-h i.v. infusion on D1, D8 and D15 in cycles of 28 days.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Zalypsis® |
| Investigational medicinal product code | PM00104 |
| Other name | |
| Pharmaceutical forms | Powder for concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

A treatment cycle consisted of the administration of three i.v. 1-h infusions of PM00104 on D1, D8 and D15. Treatment cycles were to be repeated every four weeks. PM00104 administration through a central catheter and by specialized on-site study personnel was mandatory. PM00104 was provided as a powder for concentrate for solution for infusion in only one strength of 2.5 mg per vial.

| Number of subjects in period 1 ^[1] | Dose optimization phase | Dose expansion phase |
|--|----------------------------|-------------------------|
| | | |
| Started | 22 | 13 |
| Treatment | 21 | 13 |
| Completed | 0 | 0 |
| Not completed | 22 | 13 |
| Progression disease | 9 | 6 |
| Physician decision | 2 | 3 |
| Consent withdrawn by subject | - | 2 |
| Toxicity | 2 | 1 |
| Adverse event, non-fatal | 2 | 1 |
| Death | 6 | - |
| Not treated | 1 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: There was a patient in the dose expansion phase that was excluded from all tables due to the overdose

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Dose optimization phase |
|-----------------------|-------------------------|

Reporting group description:

Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. A dose optimization phase was conducted to determine the appropriate dose of PM00104 in relapsed/refractory MM patients

| | |
|-----------------------|----------------------|
| Reporting group title | Dose expansion phase |
|-----------------------|----------------------|

Reporting group description:

Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. Once the recommended dosing had been defined, up to 37 more patients were to be recruited into the dose expansion phase in order to evaluate the anti-MM effects of PM00104. These patients were to receive single-agent PM00104 at the RD established in the earlier dose optimization phase, given as 1-h i.v. infusion on D1, D8 and D15 in cycles of 28 days.

| Reporting group values | Dose optimization phase | Dose expansion phase | Total |
|------------------------------------|-------------------------|----------------------|-------|
| Number of subjects | 22 | 13 | 35 |
| Age categorical Units: Subjects | | | |

| | | | |
|--|------------------|----------------|----|
| Age continuous Units: years median full range (min-max) | 60.5 40 to 74 | 62 50 to 76 | - |
| Gender categorical Units: Subjects | | | |
| Female | 11 | 5 | 16 |
| Male | 11 | 8 | 19 |
| Race Units: Subjects | | | |
| Caucasian | 22 | 13 | 35 |
| ECOG | | | |
| Eastern Cooperative Oncology Group | | | |
| Units: Subjects | | | |
| PS 0 | 3 | 2 | 5 |
| PS 1 | 12 | 9 | 21 |
| PS 2 | 5 | 1 | 6 |
| PS 4 | 1 | 0 | 1 |
| Unk | 1 | 1 | 2 |

End points

End points reporting groups

| | |
|---|----------------------------|
| Reporting group title | Dose optimization phase |
| Reporting group description: Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. A dose optimization phase was conducted to determine the appropriate dose of PM00104 in relapsed/refractory MM patients | |
| Reporting group title | Dose expansion phase |
| Reporting group description: Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. Once the recommended dosing had been defined, up to 37 more patients were to be recruited into the dose expansion phase in order to evaluate the anti-MM effects of PM00104. These patients were to receive single-agent PM00104 at the RD established in the earlier dose optimization phase, given as 1-h i.v. infusion on D1, D8 and D15 in cycles of 28 days. | |
| Subject analysis set title | DL1: 2.0 mg/m ² |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients treated at dose Level 1: 2.0 mg/m ² | |
| Subject analysis set title | DL2: 2.2 mg/m ² |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients treated at dose Level 2: 2.2 mg/m ² | |
| Subject analysis set title | DL3: 2.5 mg/m ² |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All patients treated at dose level 3: 2.5 mg/m ² | |

Primary: Dose-limiting toxicities

| | |
|---|--|
| End point title | Dose-limiting toxicities ^{[1][2]} |
| End point description: Number of DLTs per dose level | |
| End point type | Primary |
| End point timeframe: Dose optimization phase. Treatment period | |
| 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: This end point was conducted to determine the appropriate dose of PM00104 in relapsed/refractory MM patients. Statistical analyses do not apply because the RD was the dose level immediately below the MTD. The maximum tolerated dose (MTD) was defined as the level at which ≥33% evaluable patients have a DLT in Cycle 1.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point was conducted to determine the appropriate dose of PM00104 in relapsed/refractory MM patients and it only affects to the dose optimization phase population.

| End point values | Dose optimization phase | | | |
|-----------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 13 | | | |
| Units: percentage | | | | |
| Patients with DLT | 4 | | | |
| Patients without DLT | 9 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Response rate

| | |
|-----------------|------------------------------|
| End point title | Response rate ^[3] |
|-----------------|------------------------------|

End point description:

Response rate (CR + sCR + VGPR + PR + MR)

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Overall treatment

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Non-comparative study designed

| End point values | Dose optimization phase | Dose expansion phase | | |
|-------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 11 | | |
| Units: percentage of patients | | | | |
| Disease controlled | 11 | 7 | | |
| Disease not controlled | 6 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression-free Survival |
|-----------------|---------------------------|

End point description:

Progression-free survival, defined as the time from the start of the study treatment to PD or death (regardless of the cause of death), whichever came first

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

End point timeframe:

Overall treatment

| End point values | Dose optimization phase | Dose expansion phase | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 ^[4] | 11 ^[5] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.8 (0.9 to 3.7) | 1.8 (0.9 to 3) | | |

Notes:

[4] - Events: 14 (82.4%)

[5] - Events: 10 (90.9%)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression

| | |
|---|---------------------|
| End point title | Time to Progression |
| End point description: | |
| Time to progression, defined as the time from the start of the study treatment to PD with death due to causes other than progression censored | |
| End point type | Secondary |
| End point timeframe: | |
| Overall treatment | |

| End point values | Dose optimization phase | Dose expansion phase | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 ^[6] | 11 ^[7] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.8 (0.9 to 3.7) | 1.8 (0.9 to 3) | | |

Notes:

[6] - Events: 13 (76.5%)

[7] - Events: 10 (90.9%)

Statistical analyses

No statistical analyses for this end point

Secondary: Event-free Survival

| | |
|---|---------------------|
| End point title | Event-free Survival |
| End point description: | |
| Event-free survival, defined as the time to progression, death or treatment discontinuation, whichever came first, due to PM00104-related AEs | |
| End point type | Secondary |
| End point timeframe: | |
| Overall treatment | |

| End point values | Dose optimization phase | Dose expansion phase | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 ^[8] | 11 ^[9] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 1.9 (0.9 to 3.7) | 1.8 (0.9 to 3) | | |

Notes:

[8] - Events: 16 (94.1%)

[9] - Events: 10 (90.9%)

Statistical analyses

No statistical analyses for this end point

Secondary: Disease-free Survival

| | |
|--|-----------------------|
| End point title | Disease-free Survival |
| End point description: | |
| Disease-free survival was defined as the time from the start of CR or sCR to the time of relapse from CR/sCR | |
| End point type | Secondary |
| End point timeframe: | |
| Overall treatment | |

| End point values | Dose optimization phase | Dose expansion phase | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 ^[10] | 11 ^[11] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[10] - No patients in the study achieved CR/sCR, therefore, this parameter could not be assessed

[11] - No patients in the study achieved CR/sCR, therefore, this parameter could not be assessed

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

| | |
|--|----------------------|
| End point title | Duration of Response |
| End point description: | |
| Duration of response, defined as the duration from the first observation of response to the time of disease progression, with deaths due to causes other than progression censored | |
| End point type | Secondary |
| End point timeframe: | |
| Overall treatment | |

| End point values | Dose optimization phase | Dose expansion phase | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 ^[12] | 11 ^[13] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 2.3 (0.5 to 7.4) | 0 (0 to 0) | | |

Notes:

[12] - Events: 4 (80.0%)

[13] - No patients achieved an objective response; therefore this parameter could not be assessed

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics

| | |
|--|------------------|
| End point title | Pharmacokinetics |
| End point description: | |
| The complete plasma concentration-time profiles of PM00104 were analyzed by standard non-compartmental methods (NCA). NCA was performed using Phoenix WinNonlin v. 6.3 (Certara, USA). | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 and day 8 of cycle 1 | |

| End point values | DL1: 2.0 mg/m ² | DL2: 2.2 mg/m ² | DL3: 2.5 mg/m ² | |
|----------------------------------|----------------------------|----------------------------|----------------------------|--|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | |
| Number of subjects analysed | 17 ^[14] | 7 ^[15] | 9 ^[16] | |
| Units: units | | | | |
| arithmetic mean (standard error) | | | | |
| C _{max} (µg/L) - Day 1 | 14.9 (± 7.94) | 41.86 (± 48.46) | 22.39 (± 6.19) | |
| C _{max} (µg/L) - Day 8 | 19.8 (± 6.8) | 16.38 (± 7.98) | 28.39 (± 13.03) | |
| AUC (h*µg/L) - Day 1 | 76.42 (± 38.96) | 224.25 (± 253.18) | 111.14 (± 38.07) | |
| AUC (h*µg/L) - Day 8 | 174.61 (± 210.53) | 109.3 (± 72.6) | 112.09 (± 34.1) | |
| CL (L/h) - Day 1 | 47.03 (± 33.01) | 39.83 (± 25.19) | 44.07 (± 18.7) | |
| CL (L/h) - Day 8 | 40.26 (± 25.17) | 46.45 (± 23.32) | 41.4 (± 13.23) | |

Notes:

[14] - Day 8: N=4

[15] - Day 8: N=4

[16] - Day 8: N=6

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 11.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Dose optimization phase |
|-----------------------|-------------------------|

Reporting group description:

Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. A dose optimization phase was conducted to determine the appropriate dose of PM00104 in relapsed/refractory MM patients

| | |
|-----------------------|----------------------|
| Reporting group title | Dose expansion phase |
|-----------------------|----------------------|

Reporting group description:

Zalypsis® (PM00104) in Relapsed/Refractory Multiple Myeloma Patients. Once the recommended dosis had been defined, up to 37 more patients were to be recruited into the dose expansion phase in order to evaluate the anti-MM effects of PM00104. These patients were to receive single-agent PM00104 at the RD established in the earlier dose optimization phase, given as 1-h i.v. infusion on D1, D8 and D15 in cycles of 28 days.

| Serious adverse events | Dose optimization phase | Dose expansion phase | |
|---|-------------------------|----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 12 / 21 (57.14%) | 5 / 13 (38.46%) | |
| number of deaths (all causes) | 7 | 3 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Hepatic neoplasm malignant | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis limb | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration | | | |

| | | | |
|---|-----------------|-----------------|--|
| site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 2 / 13 (15.38%) | |
| occurrences causally related to treatment / all | 2 / 7 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung infiltration | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Gastroenteritis Escherichia coli | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 13 (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 | 1 / 21 (4.76%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| Non-serious adverse events | Dose optimization phase | Dose expansion phase | |
|---|-------------------------|----------------------|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 20 / 21 (95.24%) | 13 / 13 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) hepatic neoplasm malignant subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Tumour lysis syndrome subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 13 (7.69%) 1 | |
| Vascular disorders Haematoma subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Haemorrhage subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Hypotension subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 1 / 13 (7.69%) 1 | |
| Pallor subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 13 (0.00%) 0 | |
| Phlebitis subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 2 / 13 (15.38%) 3 | |
| Venous thrombosis limb subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| General disorders and administration site conditions | | | |

| | | | |
|---|------------------|------------------|--|
| Fatigue | | | |
| subjects affected / exposed | 13 / 21 (61.90%) | 10 / 13 (76.92%) | |
| occurrences (all) | 42 | 30 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 1 | |
| Injection site erythema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Injection site reaction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 13 (15.38%) | |
| occurrences (all) | 0 | 2 | |
| Local swelling | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 13 (15.38%) | |
| occurrences (all) | 0 | 4 | |
| Peripheral coldness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 13 / 21 (61.90%) | 4 / 13 (30.77%) | |
| occurrences (all) | 24 | 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 0 / 13 (0.00%) | |
| occurrences (all) | 11 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 13 (0.00%) | |
| occurrences (all) | 8 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 2 / 13 (15.38%) | |
| occurrences (all) | 7 | 3 | |
| Haemoptysis | | | |

| | | | |
|---|----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Productive cough subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 5 | 0 / 13 (0.00%) 0 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 5 / 21 (23.81%) 7 | 2 / 13 (15.38%) 12 | |
| Insomnia subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 13 (0.00%) 0 | |
| Investigations Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Protein S increased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Injury, poisoning and procedural complications Crushing injury of trunk subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 2 | 0 / 13 (0.00%) 0 | |
| Bundle branch block subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 2 | |
| Cardiac arrest | | | |

| | | | |
|--------------------------------------|------------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Left ventricular hypertrophy | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 13 (0.00%) | |
| occurrences (all) | 14 | 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Headache | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 0 / 13 (0.00%) | |
| occurrences (all) | 10 | 0 | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 13 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 7 / 21 (33.33%) | 2 / 13 (15.38%) | |
| occurrences (all) | 14 | 5 | |
| Somnolence | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 13 (7.69%) | |
| occurrences (all) | 2 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 12 / 21 (57.14%) | 8 / 13 (61.54%) | |
| occurrences (all) | 40 | 28 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 13 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 9 / 21 (42.86%) | 9 / 13 (69.23%) | |
| occurrences (all) | 20 | 20 | |
| Splenomegaly | | | |

| | | | |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 10 / 21 (47.62%) | 5 / 13 (38.46%) | |
| occurrences (all) | 27 | 12 | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 2 | |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 13 (15.38%) | |
| occurrences (all) | 0 | 5 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 3 | |
| Abdominal rigidity | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Aerophagia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 4 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 2 | |
| Constipation | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 6 / 13 (46.15%) | |
| occurrences (all) | 10 | 19 | |
| Diarrhoea | | | |

| | | | |
|---|------------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 6 / 21 (28.57%) 8 | 2 / 13 (15.38%) 3 | |
| Nausea subjects affected / exposed occurrences (all) | 8 / 21 (38.10%) 20 | 3 / 13 (23.08%) 14 | |
| Vomiting subjects affected / exposed occurrences (all) | 10 / 21 (47.62%) 19 | 2 / 13 (15.38%) 3 | |
| Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Hepatic pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Hepatomegaly subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 13 (7.69%) 1 | |
| Skin and subcutaneous tissue disorders Petechiae subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 13 (7.69%) 1 | |
| Pruritus subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 5 | 0 / 13 (0.00%) 0 | |
| Rash subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 6 | 0 / 13 (0.00%) 0 | |
| Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| Oliguria subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 13 (7.69%) 2 | |
| Renal failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 13 (15.38%) | |
| occurrences (all) | 0 | 3 | |
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 1 / 13 (7.69%) | |
| occurrences (all) | 11 | 3 | |
| Back pain | | | |
| subjects affected / exposed | 9 / 21 (42.86%) | 4 / 13 (30.77%) | |
| occurrences (all) | 25 | 10 | |
| Bone pain | | | |
| subjects affected / exposed | 5 / 21 (23.81%) | 2 / 13 (15.38%) | |
| occurrences (all) | 12 | 11 | |
| Groin pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Muscular weakness | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 13 (7.69%) | |
| occurrences (all) | 5 | 1 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Osteoporosis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 13 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Pain in extremity | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 6 | 2 / 13 (15.38%) 2 | |
| Infections and infestations | | | |
| Catheter site infection | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 13 (7.69%) | |
| occurrences (all) | 6 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 2 / 13 (15.38%) | |
| occurrences (all) | 6 | 6 | |
| Oral herpes | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 13 (7.69%) | |
| occurrences (all) | 3 | 1 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 13 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 12 / 21 (57.14%) | 4 / 13 (30.77%) | |
| occurrences (all) | 29 | 14 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 2 / 13 (15.38%) | |
| occurrences (all) | 2 | 4 | |
| Hyperuricaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported