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 ≥ 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 adequated laboratory values, performance status≤2, Life expectancy ≥ 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 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.

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
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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 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.	

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	60.5	62	
full range (min-max)	40 to 74	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 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.	
Subject analysis set title	DL1: 2.0 mg/m²
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients treated at dose Level 1: 2.0 mg/m²	
Subject analysis set title	DL2: 2.2 mg/m²
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients treated at dose Level 2: 2.2 mg/m²	
Subject analysis set title	DL3: 2.5 mg/m²
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients treated at dose level 3: 2.5 mg/m²	

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/m²	DL2: 2.2 mg/m²	DL3: 2.5 mg/m²	
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)				
Cmax (µg/L) - Day 1	14.9 (± 7.94)	41.86 (± 48.46)	22.39 (± 6.19)	
Cmax (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:	
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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	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Tumour lysis syndrome			
subjects affected / exposed	1 / 21 (4.76%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hypotension			
subjects affected / exposed	2 / 21 (9.52%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Pallor			
subjects affected / exposed	2 / 21 (9.52%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Phlebitis			
subjects affected / exposed	0 / 21 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	3	
Venous thrombosis limb			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	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	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Productive cough			
subjects affected / exposed	2 / 21 (9.52%)	0 / 13 (0.00%)	
occurrences (all)	5	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 21 (23.81%)	2 / 13 (15.38%)	
occurrences (all)	7	12	
Insomnia			
subjects affected / exposed	2 / 21 (9.52%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Protein S increased			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Crushing injury of trunk			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 21 (4.76%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Bundle branch block			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	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	6 / 21 (28.57%)	2 / 13 (15.38%)	
occurrences (all)	8	3	
Nausea			
subjects affected / exposed	8 / 21 (38.10%)	3 / 13 (23.08%)	
occurrences (all)	20	14	
Vomiting			
subjects affected / exposed	10 / 21 (47.62%)	2 / 13 (15.38%)	
occurrences (all)	19	3	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hepatic pain			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hepatomegaly			
subjects affected / exposed	1 / 21 (4.76%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 21 (4.76%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Pruritus			
subjects affected / exposed	2 / 21 (9.52%)	0 / 13 (0.00%)	
occurrences (all)	5	0	
Rash			
subjects affected / exposed	2 / 21 (9.52%)	0 / 13 (0.00%)	
occurrences (all)	6	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Oliguria			
subjects affected / exposed	0 / 21 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	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	3 / 21 (14.29%)	2 / 13 (15.38%)	
occurrences (all)	6	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 occurrences (all)	0 / 21 (0.00%) 0	1 / 13 (7.69%) 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