Clinical trial results:
Phase III Randomized Clinical Trial of Lurbinectedin (PM01183) versus Pegylated Liposomal Doxorubicin or Topotecan in Patients with Platinum-resistant Ovarian Cancer (CORAIL Trial)

Summary

EudraCT number	2014-005251-39
Trial protocol	HU ES CZ AT BE GB FR DE IT
Global end of trial date	12 October 2018

Results information

Result version number	v1
This version publication date	17 October 2019
First version publication date	17 October 2019

Trial information

Trial identification

Sponsor protocol code	PM1183-C-004-14

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	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	31 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2018
Global end of trial reached?	Yes
Global end of trial date	12 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine a difference in progression-free-survival (PFS) between lurbinectedin (PM01183) and pegylated liposomal doxorubicin (PLD) or topotecan in platinum-resistant ovarian cancer patients according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1.

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 patients received the following standard antiemetic prophylaxis before each treatment infusion:
• Corticosteroids (dexamethasone i.v. at least 8 mg or equivalent, or at institutional standard antiemetic doses).
• Serotonin (5-HT3) antagonists (ondansetron at least 8 mg i.v. or equivalent).
If necessary, in addition to the above, the duration of treatment with 5-HT3 antagonists and/or dexamethasone could be extended. Additional antiemetic agents could be administered as appropriate. Aprepitant and equivalent agents (e.g., fosaprepitant) were forbidden in patients treated with lurbinectedin.
For the purpose of safety evaluations, an optimal prophylaxis was defined as all the aforementioned allowed medications at their respectively maximum dose.

Evidence for comparator: -

Actual start date of recruitment	26 June 2015
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	Romania: 22
Country: Number of subjects enrolled	Spain: 86
Country: Number of subjects enrolled	United Kingdom: 31
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 40
Country: Number of subjects enrolled	Bulgaria: 10
Country: Number of subjects enrolled	Czech Republic: 10
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Italy: 94
Country: Number of subjects enrolled	United States: 79
Country: Number of subjects enrolled	Serbia: 9

Worldwide total number of subjects	442
EEA total number of subjects	354

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)	267
From 65 to 84 years	172
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

First randomization/first study treatment administration took place on 26JUN2015. The cutoff date for results was 12OCT2018.
534 patients were screened; 442 were randomized at 83 sites/12 countries. 10 patients did not receive the study treatment.

Pre-assignment

Screening details:

IC;Age≥18 years;confirmed diagnosis of unresectable epithelial ovarian, fallopian tube or primary peritoneal cancer;Platinum-resistant disease;ECOG PS≤2;Adequate hematological, renal, metabolic, and hepatic function

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	Lurbinectedin

Arm description:

3.2 mg/m2 i.v. as a 1-hour infusion on Day 1 q3wk (three weeks = one treatment cycle) through peripheral or central lines. A minimum total volume of 100 mL, diluted in 5% glucose or 0.9% sodium chloride solution for infusion, had to be used for administration through a central venous catheter; if a peripheral venous catheter was used, the minimum volume was 250 mL

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

3.2 mg/m2 i.v. as a 1-hour infusion on Day 1 q3wk (three weeks = one treatment cycle) through peripheral or central lines. A minimum total volume of 100 mL, diluted in 5% glucose or 0.9% sodium chloride solution for infusion, had to be used for administration through a central venous catheter; if a peripheral venous catheter was used, the minimum volume was 250 mL

Arm title	Control (PLD or topotecan)

Arm description:

Patients randomized to the Control arm were assigned to receive PLD if they had previously been treated with topotecan, or to receive topotecan if they had previously been treated with PLD. However, if the number of patients randomized to either PLD or topotecan reached 60% (i.e., 126 patients) of the total number of patients expected in the Control Arm, then the treatment of choice in the Control Arm would be restricted to the less frequent control drug until the end of accrual

Arm type	Active comparator
Investigational medicinal product name	PLD
Investigational medicinal product code	
Other name	Pegylated Liposomal Doxorubicin
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2 i.v. on Day 1 q4wk (four weeks = one treatment cycle), at an initial rate of 1 mg/min through peripheral or central lines. If no infusion reactions were observed, the rate of infusion could be increased to complete the administration of the drug over one hour. Total PLD doses >90 mg and ≤90 mg had to be diluted in 500 and 250 mL of 5% glucose solution for infusion, respectively

Investigational medicinal product name	Topotecan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

i.v. as a 30-min infusion on Days 1-5 q3wk (three weeks = one treatment cycle) at the following doses:
- 1.50 mg/m2 daily, for patients with calculated CrCL ≥60 mL/min.
- 1.25 mg/m2 daily, for patients with calculated CrCL between 40 and 59 mL/min.
- 0.75 mg/m2 daily, for patients with calculated CrCL between 30 and 39 mL/min.

Topotecan was administered through peripheral or central lines, and was diluted in a minimum of 50 mL of 0.9% sodium chloride or 5% glucose solution for infusion. Skipped doses of topotecan were not replaced.

Number of subjects in period 1	Lurbinectedin	Control (PLD or topotecan)
Started	221	221
Completed	0	0
Not completed	221	221
Consent withdrawn by subject	14	16
Physician decision	8	17
Treatment-related AE	10	14
Symptomatic deterioration	13	19
Death	11	3
Other	3	1
Non-treatment-related AE	8	8
Progressive disease	152	135
Not treated	2	8

Baseline characteristics

Reporting groups	
Reporting group title	Lurbinectedin
Reporting group description:	
3.2 mg/m2 i.v. as a 1-hour infusion on Day 1 q3wk (three weeks = one treatment cycle) through peripheral or central lines. A minimum total volume of 100 mL, diluted in 5% glucose or 0.9% sodium chloride solution for infusion, had to be used for administration through a central venous catheter; if a peripheral venous catheter was used, the minimum volume was 250 mL	
Reporting group title	Control (PLD or topotecan)
Reporting group description:	
Patients randomized to the Control arm were assigned to receive PLD if they had previously been treated with topotecan, or to receive topotecan if they had previously been treated with PLD. However, if the number of patients randomized to either PLD or topotecan reached 60% (i.e., 126 patients) of the total number of patients expected in the Control Arm, then the treatment of choice in the Control Arm would be restricted to the less frequent control drug until the end of accrual	

Reporting group values	Lurbinectedin	Control (PLD or topotecan)	Total
Number of subjects	221	221	442
Age categorical Units: Subjects			
18-49 years	21	35	56
50-64 years	105	106	211
≥65 years	95	80	175
Age continuous Units: years			
median	63.0	59.0	
full range (min-max)	25 to 85	28 to 87	-
Gender categorical Units: Subjects			
Female	221	221	442
Male	0	0	0
BMI			
BMI, body mass index			
Units: Subjects			
≤20 kg/m^2	26	37	63
20-25 kg/m^2	82	84	166
25-30 kg/m^2	62	51	113
>30 kg/m^2	50	49	99
Unknown	1	0	1
Race			
Some countries like France did not allow to collect race information by ethical reasons			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	2	3	5
Black or African American	6	2	8
White	192	201	393
Other	2	2	4
Not applicable	19	12	31
ECOG PS			

ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	126	123	249
PS 1	87	94	181
PS 2	8	4	12
Primary site Units: Subjects			
Ovarian	196	195	391
Fallopian	11	13	24
Peritoneal	14	13	27
Histology type Units: Subjects			
Serous/Papillary	181	199	380
Endometrioid	14	6	20
Clear cell	10	12	22
Mucinous	3	1	4
Other	13	3	16
Histologic grade Units: Subjects			
Well differentiated	16	15	31
Moderately differentiated	21	24	45
Poorly differentiated/Undifferentiated	154	143	297
Unknown	30	39	69
BRCA status Units: Subjects			
BRCA1	10	8	18
BRCA2	4	3	7
Not mutated	64	61	125
Unknown	143	149	292
Intestinal sub-occlusion Units: Subjects			
Yes	9	10	19
No	212	211	423
Clinically evident ascites Units: Subjects			
Yes	35	39	74
No	186	182	368
Radiological presence of ascites Units: Subjects			
Yes	59	71	130
No	162	150	312
Prior radiotherapy Units: Subjects			
Yes	6	5	11
No	215	216	431
Prior Cytoreductive surgery Units: Subjects			
Yes	198	204	402
No	23	17	40
Other prior surgical procedures			

Units: Subjects			
Yes	86	81	167
No	135	140	275
Weight			
Units: Kg			
median	65.8	63.0	
full range (min-max)	37.0 to 125.0	39.0 to 142.8	-
Height			
Units: cm			
median	161.0	161.0	
full range (min-max)	147 to 177	144 to 183	-
BSA			
BSA, body surface area			
Units: m^2			
median	1.7	1.7	
full range (min-max)	1.3 to 2.4	1.3 to 2.4	-
BMI			
BMI, body mass index			
Units: kg/m^2			
median	25.1	24.7	
full range (min-max)	15.0 to 47.9	14.5 to 56.5	-
First diagnosis to randomization			
Units: months			
median	23.4	20.7	
full range (min-max)	7 to 294	4 to 184	-
Sites involved			
Units: number of sites			
median	2.0	2.0	
full range (min-max)	1 to 5	1 to 7	-

Subject analysis sets

Subject analysis set title	PLD
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients randomized to the Control arm were assigned to receive PLD	
Subject analysis set title	Topotecan
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients randomized to the Control arm were assigned to receive topotecan	

Reporting group values	PLD	Topotecan	
Number of subjects	127	94	
Age categorical			
Units: Subjects			
18-49 years	18	17	
50-64 years	61	45	
≥65 years	48	32	
Age continuous			
Units: years			
median	59.0	59.5	

full range (min-max)	28 to 87	31 to 80	

Gender categorical Units: Subjects			
Female	127	94	
Male	0	0	
BMI			
BMI, body mass index			
Units: Subjects			
≤20 kg/m^2	23	14	
20-25 kg/m^2	42	42	
25-30 kg/m^2	35	16	
>30 kg/m^2	27	22	
Unknown	0	0	
Race			
Some countries like France did not allow to collect race information by ethical reasons			
Units: Subjects			
American Indian or Alaska Native	1	0	
Asian	3	0	
Black or African American	1	1	
White	116	85	
Other	2	0	
Not applicable	4	8	
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	77	46	
PS 1	47	47	
PS 2	3	1	
Primary site Units: Subjects			
Ovarian	115	80	
Fallopian	6	7	
Peritoneal	6	7	
Histology type Units: Subjects			
Serous/Papillary	111	88	
Endometrioid	3	3	
Clear cell	10	2	
Mucinous	1	0	
Other	2	1	
Histologic grade Units: Subjects			
Well differentiated	7	8	
Moderately differentiated	12	12	
Poorly differentiated/Undifferentiated	85	58	
Unknown	23	16	
BRCA status Units: Subjects			

BRCA1	5	3	
BRCA2	1	2	
Not mutated	28	33	
Unknown	93	56	
Intestinal sub-occlusion Units: Subjects			
Yes	5	5	
No	122	89	
Clinically evident ascites Units: Subjects			
Yes	25	14	
No	102	80	
Radiological presence of ascites Units: Subjects			
Yes	41	30	
No	86	64	
Prior radiotherapy Units: Subjects			
Yes	2	3	
No	125	91	
Prior Cytoreductive surgery Units: Subjects			
Yes	114	90	
No	13	4	
Other prior surgical procedures Units: Subjects			
Yes	50	31	
No	77	63	
Weight Units: Kg			
median	63.2	62.5	
full range (min-max)	39.0 to 142.8	40.0 to 114.7	
Height Units: cm			
median	161.0	161.5	
full range (min-max)	144 to 183	145 to 175	
BSA			
BSA, body surface area			
Units: m^2			
median	1.7	1.7	
full range (min-max)	1.3 to 2.4	1.4 to 2.4	
BMI			
BMI, body mass index			
Units: kg/m^2			
median	24.9	24.2	
full range (min-max)	15.9 to 56.5	14.5 to 43.1	
First diagnosis to randomization Units: months			
median	14.9	26.8	
full range (min-max)	4 to 184	4 to 103	
Sites involved			

Units: number of sites			
median	2.0	3.0	
full range (min-max)	1 to 7	1 to 7	

End points

End points reporting groups

Reporting group title	Lurbinectedin

Reporting group description:

3.2 mg/m2 i.v. as a 1-hour infusion on Day 1 q3wk (three weeks = one treatment cycle) through peripheral or central lines. A minimum total volume of 100 mL, diluted in 5% glucose or 0.9% sodium chloride solution for infusion, had to be used for administration through a central venous catheter; if a peripheral venous catheter was used, the minimum volume was 250 mL

Reporting group title	Control (PLD or topotecan)

Reporting group description:

Patients randomized to the Control arm were assigned to receive PLD if they had previously been treated with topotecan, or to receive topotecan if they had previously been treated with PLD. However, if the number of patients randomized to either PLD or topotecan reached 60% (i.e., 126 patients) of the total number of patients expected in the Control Arm, then the treatment of choice in the Control Arm would be restricted to the less frequent control drug until the end of accrual

Subject analysis set title	PLD
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients randomized to the Control arm were assigned to receive PLD

Subject analysis set title	Topotecan
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients randomized to the Control arm were assigned to receive topotecan

Primary: Progression-free Survival by Independent Review Committee

End point title	Progression-free Survival by Independent Review Committee

End point description:

End point type	Primary

End point timeframe:

Overall period

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221[1]	221[2]		
Units: months				
median (confidence interval 95%)	3.5 (2.1 to 3.7)	3.6 (2.7 to 3.8)		

Notes:

[1] - Events (%): 180 (81.4)

[2] - Events (%): 158 (71.5)

Statistical analyses

Statistical analysis title	PFS between treatments
Comparison groups	Lurbinectedin v Control (PLD or topotecan)

Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6294
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.057
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.854
upper limit	1.309

Statistical analysis title	PFS (%) at 6 months
Statistical analysis description: PFS (%) at 6 months: Lurbinectedin: 24.3 (18.4-30.7) Control: 27.5 (20.9-34.4)	
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5032
Method	Normal approximation

Statistical analysis title	PFS (%) at 12 months
Statistical analysis description: PFS (%) at 12 months: Lurbinectedin: 8.3 (4.7-13.3) Control: 7.0 (3.3-12.5)	
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6742
Method	Normal approximation

Secondary: Progression-free Survival by Investigator's Assessment	
End point title	Progression-free Survival by Investigator's Assessment
End point description: PFS, progression-free survival	
End point type	Secondary
End point timeframe: Overall period	

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221[3]	221[4]		
Units: months				
median (confidence interval 95%)	3.7 (3.6 to 3.9)	3.7 (3.5 to 4.0)		

Notes:

[3] - Events (%): 194 (87.8)

[4] - Events (%): 179 (81.0)

Statistical analyses

Statistical analysis title	PFS between treatments
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7673
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.987
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.805
upper limit	1.209

Statistical analysis title	PFS (%) at 6 months
Statistical analysis description:	
PFS (%) at 6 months (95% CI) Lurbinectedin: 29.0 (22.8-35.4) Control: 27.4 (21.3-33.9)	
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7385
Method	Normal approximation

Statistical analysis title	PFS (%) at 12 months
Statistical analysis description:	
PFS (%) at 12 months (95% CI) Lurbinectedin: 8.2 (4.8-12.7) Control: 7.5 (4.2-12.2)	

Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8245
Method	Normal approximation

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

Overall period

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221[5]	221[6]		
Units: months				
median (confidence interval 95%)	11.4 (9.0 to 14.2)	10.9 (9.3 to 12.5)		

Notes:

[5] - Events (%): 170 (76.9)

[6] - Events (%): 168 (76.0)

Statistical analyses

Statistical analysis title	OS (%) between treatments

Statistical analysis description:

OS, Overall survival

Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8021
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.956
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.772
upper limit	1.183

Statistical analysis title	OS (%) at 12 months
Statistical analysis description: OS (%) at 12 months (95% CI): Lurbinectedin: 48.2 (41.3-54.8) Control: 45.3 (38.4-52.0)	
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5515
Method	Normal approximation

Statistical analysis title	OS (%) at 24 months
Statistical analysis description: OS (%) at 24 months (95% CI): Lurbinectedin: 22.3 (16.8-28.2) Control: 22.7 (17.1-28.7)	
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9253
Method	Normal approximation

Secondary: Response Rate by Independent Review Committee	
End point title	Response Rate by Independent Review Committee
End point description: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease	
End point type	Secondary
End point timeframe: Overall period	

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	221		
Units: subjects				
CR	3	3		
PR	29	25		
SD	90	97		
PD	83	72		
Unknown	16	24		

Statistical analyses

Statistical analysis title	Overall response rate
Statistical analysis description: ORR, n (%) 95% CI Lurbinectedin: 32 (14.5) [10.1-19.8] Control: 28 (12.7) [8.6-17.8]	
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6772
Method	Fisher exact

Secondary: Response Rate by Investigator's Assessment	
End point title	Response Rate by Investigator's Assessment
End point description: CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.	
End point type	Secondary
End point timeframe: Overall period	

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	221	221		
Units: subjects				
CR	3	2		
PR	32	35		
SD	107	94		
PD	63	68		
Unknown	16	22		

Statistical analyses

Statistical analysis title	Overall response rate
Statistical analysis description: ORR, n (%) 95% CI	

Lurbinectedin: 35 (15.8) [11.3-21.3]
Control: 37 (16.7) [12.1-22.3]

Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	442
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8976
Method	Fisher exact

Secondary: Duration of Response by Independent Review Committee

End point title	Duration of Response by Independent Review Committee
End point description:	
End point type	Secondary
End point timeframe:	
Overall period	

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	28		
Units: months				
median (confidence interval 95%)	4.0 (1.9 to 5.7)	3.7 (3.6 to 7.2)		

Statistical analyses

Statistical analysis title	Duration of response between treatments
Comparison groups	Control (PLD or topotecan) v Lurbinectedin
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2631
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.406
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.769
upper limit	2.569

Secondary: Duration of Response by Investigator’s Assessment

End point title	Duration of Response by Investigator’s Assessment

End point description:

End point type	Secondary

End point timeframe:

Overall period

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	37		
Units: months				
median (confidence interval 95%)	4.3 (3.6 to 5.8)	3.7 (3.2 to 5.6)		

Statistical analyses

Statistical analysis title	Duration of response between treatments
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8276
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.743

Secondary: Best Response according to Tumor Marker Evaluation (CA-125)

End point title	Best Response according to Tumor Marker Evaluation (CA-125)

End point description:

CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

End point type	Secondary

End point timeframe:

Overall period

End point values	Lurbinectedin	Control (PLD or topotecan)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	173	165		
Units: subjects				
CR	13	3		
PR	33	29		
SD	95	94		
PD	17	16		
Unknown	15	23		

Statistical analyses

Statistical analysis title	ORR by CA-125
Statistical analysis description: ORR by CA-125, n (%) 95% CI Lurbinectedin: 46 (26.6) [20.2-33.8] Control: 32 (19.4) [13.7-26.3]	
Comparison groups	Lurbinectedin v Control (PLD or topotecan)
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1231
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Lurbinectedin

Reporting group description:

3.2 mg/m2 i.v. as a 1-hour infusion on Day 1 q3wk (three weeks = one treatment cycle) through peripheral or central lines. A minimum total volume of 100 mL, diluted in 5% glucose or 0.9% sodium chloride solution for infusion, had to be used for administration through a central venous catheter; if a peripheral venous catheter was used, the minimum volume was 250 mL

Reporting group title	Control (PLD or topotecan)

Reporting group description:

Patients randomized to the Control arm were assigned to receive PLD if they had previously been treated with topotecan, or to receive topotecan if they had previously been treated with PLD. However, if the number of patients randomized to either PLD or topotecan reached 60% (i.e., 126 patients) of the total number of patients expected in the Control Arm, then the treatment of choice in the Control Arm would be restricted to the less frequent control drug until the end of accrual

Serious adverse events	Lurbinectedin	Control (PLD or topotecan)	
Total subjects affected by serious adverse events			
subjects affected / exposed	91 / 219 (41.55%)	85 / 213 (39.91%)	
number of deaths (all causes)	170	171	
number of deaths resulting from adverse events	6	6	
Vascular disorders			
Embolism			
subjects affected / exposed	2 / 219 (0.91%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Phlebitis			
subjects affected / exposed	1 / 219 (0.46%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			

subjects affected / exposed	2 / 219 (0.91%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 219 (0.91%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 219 (0.46%)	4 / 213 (1.88%)	
occurrences causally related to treatment / all	0 / 1	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 219 (0.46%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 219 (1.37%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vessel puncture site haematoma			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			

subjects affected / exposed	0 / 219 (0.00%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 219 (0.91%)	4 / 213 (1.88%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 219 (1.37%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 219 (1.37%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonitis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	3 / 219 (1.37%)	0 / 213 (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	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			

subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorespiratory arrest			
subjects affected / exposed	3 / 219 (1.37%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	1 / 3	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 219 (0.46%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			

subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 219 (0.91%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (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 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 219 (3.65%)	12 / 213 (5.63%)	
occurrences causally related to treatment / all	11 / 14	16 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	14 / 219 (6.39%)	12 / 213 (5.63%)	
occurrences causally related to treatment / all	12 / 14	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leucopenia			
subjects affected / exposed	3 / 219 (1.37%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	3 / 3	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	11 / 219 (5.02%)	13 / 213 (6.10%)	
occurrences causally related to treatment / all	14 / 14	13 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	9 / 219 (4.11%)	11 / 213 (5.16%)	
occurrences causally related to treatment / all	9 / 9	20 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 219 (0.91%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	6 / 219 (2.74%)	6 / 213 (2.82%)	
occurrences causally related to treatment / all	0 / 8	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	4 / 219 (1.83%)	7 / 213 (3.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			

subjects affected / exposed	2 / 219 (0.91%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 219 (0.91%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	24 / 219 (10.96%)	21 / 213 (9.86%)	
occurrences causally related to treatment / all	1 / 32	0 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 219 (0.46%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nausea			
subjects affected / exposed	7 / 219 (3.20%)	4 / 213 (1.88%)	
occurrences causally related to treatment / all	5 / 8	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	10 / 219 (4.57%)	4 / 213 (1.88%)	
occurrences causally related to treatment / all	8 / 10	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis			
subjects affected / exposed	0 / 219 (0.00%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct obstruction			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 219 (0.91%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	1 / 219 (0.46%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hydronephrosis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
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			
Flank pain			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Herpes virus infection			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 219 (0.91%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 219 (0.91%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 219 (2.28%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	3 / 5	1 / 1	
deaths causally related to treatment / all	1 / 1	1 / 1	
Septic shock			
subjects affected / exposed	1 / 219 (0.46%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin infection			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	4 / 219 (1.83%)	3 / 213 (1.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 219 (0.00%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 219 (0.00%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	4 / 219 (1.83%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	1 / 4	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperclycemia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoalbuminemia			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 219 (0.46%)	2 / 213 (0.94%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 219 (0.91%)	1 / 213 (0.47%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 219 (0.46%)	0 / 213 (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	Lurbinectedin	Control (PLD or topotecan)	
Total subjects affected by non-serious adverse events subjects affected / exposed	212 / 219 (96.80%)	211 / 213 (99.06%)	
Investigations Weight decreased subjects affected / exposed occurrences (all)	10 / 219 (4.57%) 14	14 / 213 (6.57%) 16	
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	12 / 219 (5.48%) 22	4 / 213 (1.88%) 9	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Neuropathy peripheral subjects affected / exposed occurrences (all)	26 / 219 (11.87%) 36 19 / 219 (8.68%) 32	9 / 213 (4.23%) 10 15 / 213 (7.04%) 20	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leucopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	57 / 219 (26.03%) 154 23 / 219 (10.50%) 39 73 / 219 (33.33%) 167 20 / 219 (9.13%) 46	77 / 213 (36.15%) 196 21 / 213 (9.86%) 38 89 / 213 (41.78%) 211 39 / 213 (18.31%) 77	
General disorders and administration site conditions Fatigue			

subjects affected / exposed	133 / 219 (60.73%)	113 / 213 (53.05%)	
occurrences (all)	327	205	
Mucosal inflammation			
subjects affected / exposed	22 / 219 (10.05%)	68 / 213 (31.92%)	
occurrences (all)	26	145	
Oedema			
subjects affected / exposed	25 / 219 (11.42%)	13 / 213 (6.10%)	
occurrences (all)	32	15	
Pyrexia			
subjects affected / exposed	25 / 219 (11.42%)	33 / 213 (15.49%)	
occurrences (all)	29	40	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	12 / 219 (5.48%)	10 / 213 (4.69%)	
occurrences (all)	16	12	
Abdominal pain			
subjects affected / exposed	74 / 219 (33.79%)	52 / 213 (24.41%)	
occurrences (all)	145	73	
Ascites			
subjects affected / exposed	14 / 219 (6.39%)	21 / 213 (9.86%)	
occurrences (all)	15	43	
Constipation			
subjects affected / exposed	72 / 219 (32.88%)	61 / 213 (28.64%)	
occurrences (all)	118	84	
Diarrhoea			
subjects affected / exposed	44 / 219 (20.09%)	35 / 213 (16.43%)	
occurrences (all)	70	58	
Nausea			
subjects affected / exposed	156 / 219 (71.23%)	92 / 213 (43.19%)	
occurrences (all)	390	169	
Dyspepsia			
subjects affected / exposed	14 / 219 (6.39%)	15 / 213 (7.04%)	
occurrences (all)	16	16	
Vomiting			
subjects affected / exposed	86 / 219 (39.27%)	58 / 213 (27.23%)	
occurrences (all)	195	88	

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 219 (7.76%)	26 / 213 (12.21%)	
occurrences (all)	19	33	
Dyspnoea			
subjects affected / exposed	29 / 219 (13.24%)	23 / 213 (10.80%)	
occurrences (all)	37	34	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	5 / 219 (2.28%)	30 / 213 (14.08%)	
occurrences (all)	5	33	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	3 / 219 (1.37%)	51 / 213 (23.94%)	
occurrences (all)	3	95	
Rash			
subjects affected / exposed	8 / 219 (3.65%)	14 / 213 (6.57%)	
occurrences (all)	9	25	
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	22 / 219 (10.05%)	10 / 213 (4.69%)	
occurrences (all)	23	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	15 / 219 (6.85%)	5 / 213 (2.35%)	
occurrences (all)	20	7	
Back pain			
subjects affected / exposed	13 / 219 (5.94%)	19 / 213 (8.92%)	
occurrences (all)	17	22	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	11 / 219 (5.02%)	20 / 213 (9.39%)	
occurrences (all)	14	21	
Urinary tract infection			
subjects affected / exposed	21 / 219 (9.59%)	15 / 213 (7.04%)	
occurrences (all)	25	18	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	51 / 219 (23.29%)	47 / 213 (22.07%)	
occurrences (all)	80	69	
Hypokalaemia			
subjects affected / exposed	15 / 219 (6.85%)	15 / 213 (7.04%)	
occurrences (all)	26	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2015	This amendment resulted in a local version (v.1.1) of the study protocol that was only implemented in France and included the following changes: • Following a request by French Health Authorities, patients with AP levels between 2.5 and 5 × ULN were not allowed to be included into the study. • As a result of the merger between Zeltia, S.A and Pharma Mar, S.A., Sociedad Unipersonal, the Sponsor shall now be referred to as Pharma Mar, S.A, without further reference to "Sociedad Unipersonal".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: