Clinical trial results:
Evaluation of the Effect of Lurbinectedin (PM01183) on Cardiac Repolarization (QTc Duration) in Patients with Selected Solid Tumors

Summary

EudraCT number	2015-000206-18
Trial protocol	ES
Global end of trial date	19 August 2016

Results information

Result version number	v3 (current)
This version publication date	27 November 2019
First version publication date	01 April 2018
Version creation reason	• Correction of full data set The Clinical Study Report is being updated with an addendum to analyze and document Serious Adverse Events (SAEs) regardless of their relationship to the study treatment that occurred in the 39 patients treated in study PM1183-B-005-14-QT

Trial information

Trial identification

Sponsor protocol code	PM1183-B-005-14-QT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02451007
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., Pharma Mar, S.A., +34 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical Development Department of PharmaMar´s Oncology, Business Unit., Pharma Mar, S.A., +34 91846 60 00, 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	07 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 August 2016
Global end of trial reached?	Yes
Global end of trial date	19 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the potential effects of PM01183 at a therapeutic dose on the duration of the QTc interval, measured by electrocardiograms (ECGs), in patients with selected solid tumors.

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:

During their participation in the QT evaluation study, patients should receive palonosetron 0.25 mg i.v. instead of ondansetron (tropisetron 5 mg i.v. could be considered if palonosetron is not available).

Evidence for comparator:

Not applicable

Actual start date of recruitment	12 August 2015
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	United States: 14
Country: Number of subjects enrolled	Spain: 25
Worldwide total number of subjects	39
EEA total number of subjects	25

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)	37
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was nested into a multicenter clinical trial with a competitive recruitment. From August 2015 to June 2016, a total of 39 evaluable patients at 12 sites in USA and Spain were included in this QT evaluation study with baseline and one or more postbaseline ECG assessments available.

Pre-assignment

Screening details:

Inclusion:IC signed,Normal cardiac conduction/function,SBP 90-150 DBP<90 mmHg,Specific serum electrolyte levels
Exclusion:Age>65 years,PS=2,HR disturbances,Significant ischemic coronary disease, heart failure, myocardial infarction, or unstable angina within the last six months,Prior exposure to anthracyclines at a cumulative dose of doxorubicin.

Period 1

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

Blinding implementation details:

Not blinded

Arms

Arm title	PM01183

Arm description:

Lurbinectedin was administered at a dose of 3.2 mg/m² given as a 1-hour i.v. every three weeks (q3wk) (three weeks = one treatment cycle). QTc interval duration was assessed when the patient was treated with lurbinectedin for the first time.

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	PM01183
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Lurbinectedin was administered at a dose of 3.2 mg/m² given as a 1-hour i.v. every three weeks (q3wk) (three weeks = one treatment cycle).

Number of subjects in period 1	PM01183
Started	39
Completed	32
Not completed	7
Patient's refusal	4
Adverse event, serious fatal	1
Disease progression	2

Baseline characteristics

Reporting groups	
Reporting group title	PM01183
Reporting group description:	
Lurbinectedin was administered at a dose of 3.2 mg/m² given as a 1-hour i.v. every three weeks (q3wk) (three weeks = one treatment cycle). QTc interval duration was assessed when the patient was treated with lurbinectedin for the first time.	

Reporting group values	PM01183	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
18-42 years	5	5	
43-65 years	34	34	
Age continuous Units: years			
median	56		
full range (min-max)	28 to 65	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	17	17	
Physical examination Units: Subjects			
Normal	32	32	
Abnormal	7	7	
ECOG PS			
ECOG PS, Eastern Cooperative Oncology group performance status			
Units: Subjects			
PS 0	17	17	
PS 1	22	22	
ECG			
ECG, electrocardiogram			
Units: Subjects			
Normal	29	29	
Non-significant abnormalities	10	10	
Tumor type Units: Subjects			
Endometrial carcinoma	9	9	
Head and neck carcinoma	6	6	
Neuroendocrine tumors	5	5	
Small cell lung cancer	5	5	
Biliary tract carcinoma	4	4	
Ewing's family of tumors	3	3	
Germ cell tumor	3	3	
BRCA 1/2-associated metastatic breast carcinoma	2	2	
Carcinoma of unknown primary site	2	2	

Previous anthracyclines Units: Subjects			
Yes	6	6	
No	33	33	
Weight Units: kg			
median	76		
full range (min-max)	42.9 to 115.0	-	
Height Units: cm			
median	169.0		
full range (min-max)	149.0 to 187.0	-	
BSA			
BSA, body surface area;			
Units: m2			
median	1.9		
full range (min-max)	1.4 to 2.3	-	
Heart rate			
bpm, beats per minute			
Units: bpm			
median	76		
full range (min-max)	56 to 103	-	
SBP			
SBP, Systolic blood pressure			
Units: mmHg			
median	123		
full range (min-max)	93 to 147	-	
DBP			
DBP, Diastolic blood pressure			
Units: mmHg			
median	74		
full range (min-max)	56 to 86	-	
Body temperature Units: Cº			
median	36.6		
full range (min-max)	35.0 to 37.3	-	
LVEF - ECHO			
LVEF, left ventricular ejection fraction; ECHO; echocardiography			
Units: percent			
median	62.0		
full range (min-max)	50.0 to 75.0	-	
LVEF - MUGA			
LVEF, left ventricular ejection fraction; MUGA, multiple-gated acquisition scan			
Units: percent			
median	65.5		
full range (min-max)	56.0 to 67.0	-	

End points

End points reporting groups

Reporting group title	PM01183

Reporting group description:

Lurbinectedin was administered at a dose of 3.2 mg/m² given as a 1-hour i.v. every three weeks (q3wk) (three weeks = one treatment cycle). QTc interval duration was assessed when the patient was treated with lurbinectedin for the first time.

Primary: Change in QTcF (By Time Point)

End point title	Change in QTcF (By Time Point)[1]

End point description:

QTCF,QT corrected according to Fridericia's formula; ΔQTCF,Change in QTcF; EOI, end of infusion
On Day 1 (D1) of Cycle 1 (C1), all LSM ΔQTcF had low positive values, without any clear trend to change with time. On D2, D4, D8 of C1, LSM ΔQTcF systematically dropped to values below zero; from -12.4 ms in D3 to -5.2 in D8.
On D1 of C2, LSM ΔQTcF at all time points were slightly larger than those on D1 of C1, with the largest at 3 hour after EOI time point. As in Cycle 1, LSM ΔQTcF posterior to D1 (only D8 in C2) was below zero. Therefore, the upper bound (UB) of the (two-sided) 90%CI at all time points were less than the protocol-specified cut-off of 20 ms at each time point t. Specifically, the maximum LSM ΔQTcF occurred 3 hour after the end of C2 infusion: LSM ΔQTcF=5.4 ms (90%CI, 1.2, 9.6). At all other time points, LSM ΔQTcF were ≤3.3 ms, and UB of the 90%CI were <6.6 ms. Thus, non-inferiority of any ECG time point t to baseline with respect of QTc prolongation can be concluded

End point type	Primary

End point timeframe:

Overall 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: Non-comparative design. The primary objective of this study was to assess the potential effects of lurbinectedin at a therapeutic dose on the duration of the QTc interval, measured by electrocardiograms (ECGs), in patients with selected solid tumors

End point values	PM01183			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: ms				
least squares mean (confidence interval 90%)				
Cycle 1 - 5 min before EOI	3.32 (1.12 to 5.51)			
Cycle 1 - 30 min after EOI	1.76 (-0.41 to 3.93)			
Cycle 1 - 1 hour after EOI	1.84 (-1.02 to 4.69)			
Cycle 1 - 3 hour after EOI	1.32 (-1.40 to 4.05)			
Cycle 1 - 24 hour after EOI	-8.24 (-11.2 to -5.26)			
Cycle 1 - 72 hour after EOI	-12.4 (-15.4 to -9.39)			
Cycle 1 - 168 hour after EOI	-5.20 (-7.98 to -2.41)			
Cycle 2 - Before start of infusion	-0.46 (-3.27 to 2.35)			

Cycle 2 - 5 min before EOI	2.25 (-1.18 to 5.68)			
Cycle 2 - 30 min after EOI	2.32 (-1.02 to 5.66)			
Cycle 2 - 1 hour after EOI	2.73 (-1.08 to 6.54)			
Cycle 2 - 3 hour after EOI	5.39 (1.17 to 9.60)			
Cycle 2 - 168 hour after EOI	-4.22 (-7.36 to -1.08)			

Statistical analyses

No statistical analyses for this end point

Primary: Change in QTcF (categorical)

End point title	Change in QTcF (categorical)[2]

End point description:

EOI, end of infusion; ms, milliseconds; ΔQTcF, change from baseline in QT corrected according to Fridericia's formula;
ΔQTcF in all patients at all time points were ≤30 ms, except for a male patient older than 42 years (patient #44016) who had a ΔQTcF longer than 30 ms, which occurred in Cycle 2, 3 hour after EOI. No ΔQTcF > 60 ms were observed.

End point type	Primary

End point timeframe:

Overall period

Notes:

[2] - 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 design. The primary objective of this study was to assess the potential effects of lurbinectedin at a therapeutic dose on the duration of the QTc interval, measured by electrocardiograms (ECGs), in patients with selected solid tumors

End point values	PM01183			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: subjects	39			

Statistical analyses

No statistical analyses for this end point

Secondary: Relationship between ΔQTcF and time-matched lurbinectedin plasma concentrations

End point title	Relationship between ΔQTcF and time-matched lurbinectedin plasma concentrations

End point description:

Linear mixed effects model to quantify the relationship between the lurbinectedin plasma concentrations and ΔQTcF and Predicted ΔQTcF and 90% CI at mean lurbinectedin Cmax.

The slope was estimated to be 2.06 and its 90% CI did not include zero ($p<0.0001$), thus indicating an apparent relationship between lurbinectedin plasma concentrations and ΔQTcF. The slope value is likely

to be affected by negative ΔQTcF values at low lurbinectedin concentrations rather than to large ΔQTcF values at large lurbinectedin concentrations.

The predicted ΔQTcF and its two-sided 90% CI at the highest clinically relevant lurbinectedin exposure (mean Cmax of 105 ng/mL). The UB of the CI (5.10) is below the 10 ms threshold set at the ICH E14 Q&A R3.

End point type	Secondary

End point timeframe:

Overall period

End point values	PM01183			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: µg/mL				
number (confidence interval 90%)				
Intercept	-6.4 (-8.44 to -4.35)			
Plasma concentration (µg/mL)	2.06 (1.42 to 2.71)			
Predicted ΔQTcF	2.94 (0.79 to 5.10)			

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	16.0

Reporting groups	
Reporting group title	PM01183

Reporting group description:

Lurbinectedin was administered at a dose of 3.2 mg/m² given as a 1-hour i.v. every three weeks (q3wk) (three weeks = one treatment cycle).

Serious adverse events	PM01183		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 39 (23.08%)		
number of deaths (all causes)	13		
number of deaths resulting from adverse events	1		
Investigations			
Blood calcium decreased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood phosphorus decreased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Facial paralysis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aspiration			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin infection			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PM01183		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 39 (89.74%)		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Neutropenia			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	9		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	15 / 39 (38.46%)		
occurrences (all)	25		
Pyrexia			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	4		
Gastrointestinal disorders			

Abdominal pain subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 10		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Constipation subjects affected / exposed occurrences (all)	8 / 39 (20.51%) 10		
Nausea subjects affected / exposed occurrences (all)	19 / 39 (48.72%) 28		
Vomiting subjects affected / exposed occurrences (all)	7 / 39 (17.95%) 9		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4		
Hyponatraemia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2015	This protocol amendment included the following changes: - Altered levels of both corrected serum calcium and ionic calcium may be related to alterations in the length of the QT interval. Corrected serum calcium level is a routine parameter, whereas measurement of ionic calcium may not be available at some study sites. Hence, inclusion criterion #5 was amended to request the measurement of corrected serum calcium instead of ionic calcium. - The protocol of clinical trial PM1183-B-005-14 was amended to change the lurbinectedin starting dose from 4 mg/m² to 3.2 mg/m² and to stop giving primary prophylaxis with colony-stimulating factors. Therefore, these changes were also applicable to the protocol of study PM1183-B-005-14-QT. - The timing of ECG recording and blood sample collection during screening, and during and after lurbinectedin infusion, was clarified. - A turnaround time of 72 hours was set for ECG reporting to the Central ECG Laboratory, except for the screening ECG, which had to be available for review within 24 hours; this was to expand the screening time window. - In Appendix 1, the lists of drugs that prolong the QT interval and/or induce torsades de pointes ventricular arrhythmia were updated, following the inclusion of new drugs in the website www.azcert.org. - In Appendix 2, a typographic error in the figure showing the timing of ECG collection and related procedures of the QT evaluation study was corrected. - Study contact details were updated, and some minor typographic mistakes were corrected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported