# 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 | v2 |
| This version publication date | 19 December 2018 |
| First version publication date | 01 April 2018 |
| Version creation reason | • Correction of full data set<br>Correction of data in section End point/Secondary: PK/PD Analysis. |

## 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<br>Units: Subjects | | | |
| 18-42 years | 5 | 5 | |
| 43-65 years | 34 | 34 | |
| Age continuous<br>Units: years | | | |
| median | 56 | | |
| full range (min-max) | 28 to 65 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 22 | 22 | |
| Male | 17 | 17 | |
| Physical examination<br>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<br>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<br>Units: Subjects | | | |
| Yes | 6 | 6 | |
| No | 33 | 33 | |
| Weight<br>Units: kg | | | |
| median | 76 | | |
| full range (min-max) | 42.9 to 115.0 | - | |
| Height<br>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<br>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 / 2 | | |
| 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 | | | |
| VIIth nerve 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 / 2 | | |
| 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<br>subjects affected / exposed<br>occurrences (all) | 6 / 39 (15.38%)<br>10 | | |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all) | 3 / 39 (7.69%)<br>3 | | |
| Constipation<br>subjects affected / exposed<br>occurrences (all) | 8 / 39 (20.51%)<br>10 | | |
| Nausea<br>subjects affected / exposed<br>occurrences (all) | 19 / 39 (48.72%)<br>28 | | |
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 7 / 39 (17.95%)<br>9 | | |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | 3 / 39 (7.69%)<br>3 | | |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 3 / 39 (7.69%)<br>3 | | |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 4 / 39 (10.26%)<br>4 | | |
| Hyponatraemia<br>subjects affected / exposed<br>occurrences (all) | 2 / 39 (5.13%)<br>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:<br>- 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.<br>- 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.<br>- The timing of ECG recording and blood sample collection during screening, and during and after lurbinectedin infusion, was clarified.<br>- 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.<br>- 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.<br>- 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.<br>- 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