



## Clinical trial results:

### A Phase II Study of PM01183 as Second-line Treatment in Patients with Metastatic Pancreatic Cancer.

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2010-024292-30   |
| Trial protocol           | GB ES            |
| Global end of trial date | 28 November 2013 |

#### Results information

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

#### Trial information

##### Trial identification

|                       |                 |
|-----------------------|-----------------|
| Sponsor protocol code | PM1183-B-001-10 |
|-----------------------|-----------------|

##### 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-Norte, Colmenar Viejo, Madrid, Spain, 28770                                        |
| Public contact               | Clinical Development Department of PharmaMar's Oncology, Business Unit., Pharma Mar, S.A., +34 918466000, clinicaltrials@pharmamar.com |
| Scientific contact           | Clinical Development Department of PharmaMar's Oncology, Business Unit., Pharma Mar, S.A., +34 918466000, clinicaltrials@pharmamar.com |

Notes:

#### Paediatric regulatory details

|                                                                      |    |
|----------------------------------------------------------------------|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|                                                      |                   |
|------------------------------------------------------|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 18 September 2015 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 28 November 2013  |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 28 November 2013  |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the antitumor activity of PM01183 in terms of overall survival rate at 6 months (OS6) in patients with metastatic pancreatic cancer.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and was consistent with the Good Clinical Practice (GCP) and applicable regulatory requirements. Study personnel involved in conducting this trial was qualified by education, training, and experience to perform their respective task(s).

The Sponsor provided insurance or indemnity in accordance with the applicable regulatory requirements.

Background therapy:

All patients had to receive standard prophylactic medication at least 30 minutes before the administration of PM01183, as follows:

- Corticosteroids (dexamethasone 8 mg i.v. or equivalent)
- Serotonin (5-HT<sub>3</sub>) antagonists (ondansetron 8 mg i.v. or equivalent)

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 29 June 2011 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Spain: 33          |
| Country: Number of subjects enrolled | United Kingdom: 12 |
| Worldwide total number of subjects   | 45                 |
| EEA total number of subjects         | 45                 |

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)      | 26 |
| From 65 to 84 years       | 19 |
| 85 years and over         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 45 patients were enrolled at seven investigational sites, and 44 of them were treated with PM01183. The patients participated in this study between 29 June 2011 (first consent) and 28 November 2013 (last follow-up). First and last infusions were administered on 11 July 2011 and 3 July 2013, respectively

### Pre-assignment

Screening details:

Voluntary written IC, 18-75 years, Histologically/cytologically confirmed cancer of the exocrine pancreas, Stage IV disease, Patient had to have progressed during or after one prior line of gemcitabine based therapy, ECOG PS  $\leq$  1, Adequate hematological, renal, metabolic and hepatic function, At least two weeks since last prior therapy

### Period 1

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

### Arms

|                  |         |
|------------------|---------|
| <b>Arm title</b> | PM01183 |
|------------------|---------|

Arm description:

PM01183 was given at a dose of 7.0 mg FD as a 1-hour q3wk i.v. infusion. Each cycle lasted three weeks.

|                                        |                                                  |
|----------------------------------------|--------------------------------------------------|
| Arm type                               | Experimental                                     |
| Investigational medicinal product name | PM01183                                          |
| 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:

PM01183 was given at a dose of 7.0 mg FD as a 1-hour q3wk i.v. infusion. Each cycle lasted three weeks

|                                       |         |
|---------------------------------------|---------|
| <b>Number of subjects in period 1</b> | PM01183 |
| Started                               | 45      |
| Treated                               | 44      |
| Completed                             | 0       |
| Not completed                         | 45      |
| Adverse event, serious fatal          | 3       |
| Clinical progression                  | 2       |
| Consent withdrawn by subject          | 1       |
| Physician decision                    | 1       |
| Adverse event, non-fatal              | 1       |

|                                |    |
|--------------------------------|----|
| Clinical deterioration         | 1  |
| Death due to malignant disease | 5  |
| Progressive disease            | 30 |
| Not treated                    | 1  |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Overall period |
|-----------------------|----------------|

Reporting group description: -

| Reporting group values                                | Overall period | Total |  |
|-------------------------------------------------------|----------------|-------|--|
| Number of subjects                                    | 45             | 45    |  |
| Age categorical                                       |                |       |  |
| Units: Subjects                                       |                |       |  |
| 18-49 years                                           | 2              | 2     |  |
| 50-69 years                                           | 36             | 36    |  |
| >=70 years                                            | 7              | 7     |  |
| Age continuous                                        |                |       |  |
| Units: years                                          |                |       |  |
| median                                                | 62             |       |  |
| full range (min-max)                                  | 42 to 83       | -     |  |
| Gender categorical                                    |                |       |  |
| Units: Subjects                                       |                |       |  |
| Female                                                | 32             | 32    |  |
| Male                                                  | 13             | 13    |  |
| Race                                                  |                |       |  |
| Units: Subjects                                       |                |       |  |
| Caucasian                                             | 42             | 42    |  |
| Black                                                 | 1              | 1     |  |
| Arabic                                                | 2              | 2     |  |
| ECOG                                                  |                |       |  |
| Eastern Cooperative Oncology Group performance status |                |       |  |
| Units: Subjects                                       |                |       |  |
| PS 0                                                  | 8              | 8     |  |
| PS 1                                                  | 37             | 37    |  |
| Elevated CA19-9                                       |                |       |  |
| Units: Subjects                                       |                |       |  |
| Yes                                                   | 41             | 41    |  |
| No                                                    | 4              | 4     |  |
| Pain control medication                               |                |       |  |
| Units: Subjects                                       |                |       |  |
| Fully controlled                                      | 9              | 9     |  |
| Controlled most of the time                           | 19             | 19    |  |
| Controlled < 50% of time                              | 3              | 3     |  |
| No                                                    | 14             | 14    |  |
| Opioid consumption                                    |                |       |  |
| Units: Subjects                                       |                |       |  |
| Yes                                                   | 16             | 16    |  |
| No                                                    | 29             | 29    |  |
| Primary tumor location (pancreas)                     |                |       |  |
| Units: Subjects                                       |                |       |  |
| Head                                                  | 28             | 28    |  |

|                                                              |    |    |  |
|--------------------------------------------------------------|----|----|--|
| Body/tail                                                    | 16 | 16 |  |
| Head + body/tail                                             | 1  | 1  |  |
| Tumor stage at diagnosis<br>Units: Subjects                  |    |    |  |
| Metastatic                                                   | 23 | 23 |  |
| Locally advanced                                             | 17 | 17 |  |
| Early                                                        | 5  | 5  |  |
| Histology grade<br>Units: Subjects                           |    |    |  |
| Well differentiated                                          | 4  | 4  |  |
| Moderately differentiated                                    | 11 | 11 |  |
| Poorly differentiated                                        | 7  | 7  |  |
| UK                                                           | 23 | 23 |  |
| Current disease (metastatic)<br>Units: Subjects              |    |    |  |
| Visceral                                                     | 19 | 19 |  |
| Ganglionic/Peritoneal                                        | 8  | 8  |  |
| Both                                                         | 18 | 18 |  |
| No. of sites of disease<br>Units: Subjects                   |    |    |  |
| 1 site                                                       | 10 | 10 |  |
| 2 sites                                                      | 19 | 19 |  |
| 3 sites                                                      | 10 | 10 |  |
| 4 sites                                                      | 5  | 5  |  |
| 8 sites                                                      | 1  | 1  |  |
| Chemoradiotherapy<br>Units: Subjects                         |    |    |  |
| Yes                                                          | 7  | 7  |  |
| No                                                           | 38 | 38 |  |
| Surgery<br>Units: Subjects                                   |    |    |  |
| Yes                                                          | 24 | 24 |  |
| No                                                           | 21 | 21 |  |
| Setting of Chemotherapy<br>Units: Subjects                   |    |    |  |
| Advanced                                                     | 34 | 34 |  |
| Adjuvant                                                     | 9  | 9  |  |
| Adjuvant+advanced                                            | 2  | 2  |  |
| Most frequent prior chemotherapy regimens<br>Units: Subjects |    |    |  |
| Gemcitabine                                                  | 15 | 15 |  |
| Gemcitabine + capecitabine                                   | 8  | 8  |  |
| Gemcitabine + oxaliplatin                                    | 8  | 8  |  |
| Gemcitabine + paclitaxel                                     | 4  | 4  |  |
| Gemcitabine + 5-FU                                           | 3  | 3  |  |
| Gemcitabine + Others                                         | 7  | 7  |  |
| Best response to last prior chemotherapy<br>Units: Subjects  |    |    |  |
| PR                                                           | 4  | 4  |  |
| SD                                                           | 15 | 15 |  |

|                                                                                 |               |    |  |
|---------------------------------------------------------------------------------|---------------|----|--|
| PD                                                                              | 10            | 10 |  |
| NA                                                                              | 5             | 5  |  |
| UK                                                                              | 11            | 11 |  |
| Signs and symptoms                                                              |               |    |  |
| Units: Subjects                                                                 |               |    |  |
| 0 sign/symptom                                                                  | 8             | 8  |  |
| 1 sign/symptom                                                                  | 16            | 16 |  |
| 2 signs/symptoms                                                                | 10            | 10 |  |
| 3 signs/symptoms                                                                | 6             | 6  |  |
| 4 signs/symptoms                                                                | 4             | 4  |  |
| 5 signs/symptoms                                                                | 1             | 1  |  |
| Physical examination                                                            |               |    |  |
| Units: Subjects                                                                 |               |    |  |
| Normal                                                                          | 41            | 41 |  |
| Abnormal                                                                        | 4             | 4  |  |
| ECG                                                                             |               |    |  |
| Electrocardiogram                                                               |               |    |  |
| Units: Subjects                                                                 |               |    |  |
| Normal                                                                          | 32            | 32 |  |
| Abnormal                                                                        | 13            | 13 |  |
| LVEF                                                                            |               |    |  |
| left ventricular ejection fraction                                              |               |    |  |
| Units: Subjects                                                                 |               |    |  |
| Normal                                                                          | 44            | 44 |  |
| Abnormal                                                                        | 1             | 1  |  |
| BSA                                                                             |               |    |  |
| body surface area                                                               |               |    |  |
| Units: m2                                                                       |               |    |  |
| median                                                                          | 1.76          |    |  |
| full range (min-max)                                                            | 1.29 to 2.44  | -  |  |
| Albumin                                                                         |               |    |  |
| Units: g/dl                                                                     |               |    |  |
| median                                                                          | 3.9           |    |  |
| full range (min-max)                                                            | 2.6 to 4.9    | -  |  |
| CA19-9                                                                          |               |    |  |
| Units: IU/l                                                                     |               |    |  |
| median                                                                          | 1965          |    |  |
| full range (min-max)                                                            | 0.6 to 153230 | -  |  |
| Time from diagnosis to first PM01183 infusion                                   |               |    |  |
| Units: months                                                                   |               |    |  |
| median                                                                          | 7.3           |    |  |
| full range (min-max)                                                            | 2.5 to 34.8   | -  |  |
| Time from last disease progression before study entry to first PM01183 infusion |               |    |  |
| Units: months                                                                   |               |    |  |
| median                                                                          | 0.7           |    |  |
| full range (min-max)                                                            | 0.1 to 11.1   | -  |  |
| No. of sites of disease                                                         |               |    |  |
| Units: sites                                                                    |               |    |  |
| median                                                                          | 2             |    |  |



|                                         |               |   |  |
|-----------------------------------------|---------------|---|--|
| full range (min-max)                    | 1 to 8        | - |  |
| No. of agents of Chemotherapy           |               |   |  |
| Units: No. of agents                    |               |   |  |
| median                                  | 2             |   |  |
| full range (min-max)                    | 1 to 3        | - |  |
| TTP to last prior advanced chemotherapy |               |   |  |
| Units: months                           |               |   |  |
| median                                  | 4.6           |   |  |
| full range (min-max)                    | 1.4 to 23.4   | - |  |
| Signs and symptoms                      |               |   |  |
| Units: signs and symptoms               |               |   |  |
| median                                  | 1             |   |  |
| full range (min-max)                    | 0 to 5        | - |  |
| Weight                                  |               |   |  |
| Units: kilogram(s)                      |               |   |  |
| median                                  | 68.7          |   |  |
| full range (min-max)                    | 38.5 to 113.5 | - |  |
| Height                                  |               |   |  |
| Units: cm                               |               |   |  |
| median                                  | 168           |   |  |
| full range (min-max)                    | 151 to 193    | - |  |
| BMI                                     |               |   |  |
| body mass index                         |               |   |  |
| Units: kg/m2                            |               |   |  |
| median                                  | 24.1          |   |  |
| full range (min-max)                    | 16.9 to 36.8  | - |  |
| WBC                                     |               |   |  |
| Units: x10 <sup>9</sup> /l              |               |   |  |
| median                                  | 6.8           |   |  |
| full range (min-max)                    | 3.3 to 15.7   | - |  |
| Hemoglobin                              |               |   |  |
| Units: g/dl                             |               |   |  |
| median                                  | 12.1          |   |  |
| full range (min-max)                    | 9.5 to 14.9   | - |  |
| Platelets                               |               |   |  |
| Units: x10 <sup>9</sup> /l              |               |   |  |
| median                                  | 248           |   |  |
| full range (min-max)                    | 110 to 571    | - |  |
| Neutrophils                             |               |   |  |
| Units: x10 <sup>9</sup> /l              |               |   |  |
| median                                  | 4.1           |   |  |
| full range (min-max)                    | 1.7 to 12.2   | - |  |
| Lymphocytes                             |               |   |  |
| Units: x10 <sup>9</sup> /l              |               |   |  |
| median                                  | 1.5           |   |  |
| full range (min-max)                    | 0.6 to 4      | - |  |
| ALT                                     |               |   |  |
| Units: xULN                             |               |   |  |
| median                                  | 0.6           |   |  |
| full range (min-max)                    | 0.2 to 2.8    | - |  |
| AP                                      |               |   |  |

|                                                                     |                     |   |  |
|---------------------------------------------------------------------|---------------------|---|--|
| Units: xULN<br>median<br>full range (min-max)                       | 1.2<br>0.4 to 3.8   | - |  |
| AST<br>Units: xULN<br>median<br>full range (min-max)                | 0.7<br>0.4 to 3.7   | - |  |
| CPK<br>Units: xULN<br>median<br>full range (min-max)                | 0.3<br>0.1 to 1.9   | - |  |
| Creatinine<br>Units: xULN<br>median<br>full range (min-max)         | 0.6<br>0.4 to 1     | - |  |
| GGT<br>Units: xULN<br>median<br>full range (min-max)                | 1.4<br>0.3 to 21.6  | - |  |
| Total bilirubin<br>Units: xULN<br>median<br>full range (min-max)    | 0.5<br>0.2 to 1.7   | - |  |
| Calcium<br>Units: mmol/l<br>median<br>full range (min-max)          | 2.3<br>2.1 to 2.7   | - |  |
| Potassium<br>Units: mmol/l<br>median<br>full range (min-max)        | 4.2<br>3.6 to 5.3   | - |  |
| Sodium<br>Units: mmol/l<br>median<br>full range (min-max)           | 139<br>127 to 144.5 | - |  |
| Total cholesterol<br>Units: mg/dl<br>median<br>full range (min-max) | 177.9<br>85 to 249  | - |  |

## End points

### End points reporting groups

|                                                                                                                                         |         |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------|
| Reporting group title                                                                                                                   | PM01183 |
| Reporting group description:<br>PM01183 was given at a dose of 7.0 mg FD as a 1-hour q3wk i.v. infusion. Each cycle lasted three weeks. |         |

### Primary: Overall Survival Rate at Six Months

|                        |                                                    |
|------------------------|----------------------------------------------------|
| End point title        | Overall Survival Rate at Six Months <sup>[1]</sup> |
| End point description: |                                                    |

|                                                                                 |         |
|---------------------------------------------------------------------------------|---------|
| End point type                                                                  | Primary |
| End point timeframe:<br>Six months after the first PM01183 dose of each patient |         |

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: Primary endpoint (OS6) to test the null hypothesis that 25% or less patients were alive six months after the first infusion

| End point values            | PM01183           |  |  |  |
|-----------------------------|-------------------|--|--|--|
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 43 <sup>[2]</sup> |  |  |  |
| Units: Subjects             |                   |  |  |  |
| Yes                         | 14                |  |  |  |
| No                          | 29                |  |  |  |

Notes:

[2] - OS6 was thus 32.6% (95% CI: 19.1-48.5%)

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Response Rate

|                        |                       |
|------------------------|-----------------------|
| End point title        | Overall Response Rate |
| End point description: |                       |

NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease

Response rate (95% CI) (patients evaluable for efficacy, n=43) 2.3% (0.1-12.3%)

Response rate (95% CI) (patients evaluable for response, n=42) 2.4% (0.1-12.6%) (One patient died due to toxicity before the first tumor evaluation and was excluded from the population of patients evaluable for response)

|                                        |           |
|----------------------------------------|-----------|
| End point type                         | Secondary |
| End point timeframe:<br>Overall period |           |

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | PM01183         |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 43              |  |  |  |
| Units: Subjects             |                 |  |  |  |
| PR                          | 1               |  |  |  |
| SD                          | 15              |  |  |  |
| PD                          | 26              |  |  |  |
| NE                          | 1               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-free Survival

|                        |                           |
|------------------------|---------------------------|
| End point title        | Progression-free Survival |
| End point description: |                           |
| End point type         | Secondary                 |
| End point timeframe:   |                           |
| Overall period         |                           |

|                                  |                   |  |  |  |
|----------------------------------|-------------------|--|--|--|
| <b>End point values</b>          | PM01183           |  |  |  |
| Subject group type               | Reporting group   |  |  |  |
| Number of subjects analysed      | 43 <sup>[3]</sup> |  |  |  |
| Units: months                    |                   |  |  |  |
| median (confidence interval 95%) | 1.4 (1.2 to 2.3)  |  |  |  |

Notes:

[3] - Events (%) 40 (93.0%)

|                                   |                                                    |
|-----------------------------------|----------------------------------------------------|
| <b>Attachments (see zip file)</b> | Kaplan-Meier plot of progression-free survival.bmp |
|-----------------------------------|----------------------------------------------------|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Progression-free survival Rates

|                                                      |                                 |
|------------------------------------------------------|---------------------------------|
| End point title                                      | Progression-free survival Rates |
| End point description:                               |                                 |
| End point type                                       | Secondary                       |
| End point timeframe:                                 |                                 |
| at Three and Six Months after the first PM01183 dose |                                 |

|                                           |                    |  |  |  |
|-------------------------------------------|--------------------|--|--|--|
| <b>End point values</b>                   | PM01183            |  |  |  |
| Subject group type                        | Reporting group    |  |  |  |
| Number of subjects analysed               | 43                 |  |  |  |
| Units: percentage                         |                    |  |  |  |
| arithmetic mean (confidence interval 95%) |                    |  |  |  |
| PFS3                                      | 27.5 (14.1 to 41)  |  |  |  |
| PFS6                                      | 14.6 (3.6 to 25.6) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

|                        |                  |
|------------------------|------------------|
| End point title        | Overall Survival |
| End point description: |                  |
| End point type         | Secondary        |
| End point timeframe:   |                  |
| Overall period         |                  |

|                                           |                   |  |  |  |
|-------------------------------------------|-------------------|--|--|--|
| <b>End point values</b>                   | PM01183           |  |  |  |
| Subject group type                        | Reporting group   |  |  |  |
| Number of subjects analysed               | 43 <sup>[4]</sup> |  |  |  |
| Units: months                             |                   |  |  |  |
| arithmetic mean (confidence interval 95%) | 4 (3.1 to 5.4)    |  |  |  |

Notes:

[4] - Events (%): 41 (95.3%)

|                                   |                                           |
|-----------------------------------|-------------------------------------------|
| <b>Attachments (see zip file)</b> | Kaplan-Meier plot of overall survival.bmp |
|-----------------------------------|-------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival Rate

|                        |                       |
|------------------------|-----------------------|
| End point title        | Overall Survival Rate |
| End point description: |                       |

|                                                                   |           |
|-------------------------------------------------------------------|-----------|
| End point type                                                    | Secondary |
| End point timeframe:<br>at 12 Months after the first PM01183 dose |           |

|                                           |                 |  |  |  |
|-------------------------------------------|-----------------|--|--|--|
| <b>End point values</b>                   | PM01183         |  |  |  |
| Subject group type                        | Reporting group |  |  |  |
| Number of subjects analysed               | 43              |  |  |  |
| Units: percentage                         |                 |  |  |  |
| arithmetic mean (confidence interval 95%) | 9.3 (0.6 to 18) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Evolution of Tumor Marker CA19-9

|                        |                                  |
|------------------------|----------------------------------|
| End point title        | Evolution of Tumor Marker CA19-9 |
| End point description: |                                  |

|                                          |           |
|------------------------------------------|-----------|
| End point type                           | Secondary |
| End point timeframe:<br>During Treatment |           |

|                             |                   |  |  |  |
|-----------------------------|-------------------|--|--|--|
| <b>End point values</b>     | PM01183           |  |  |  |
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 35 <sup>[5]</sup> |  |  |  |
| Units: Subjects             |                   |  |  |  |
| Decrease                    | 14                |  |  |  |
| No decrease                 | 21                |  |  |  |

Notes:

[5] - High CA19-9 levels at baseline

|                                   |                      |
|-----------------------------------|----------------------|
| <b>Attachments (see zip file)</b> | CA19-9 variation.bmp |
|-----------------------------------|----------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetic parameters (CL)

|                        |                                 |
|------------------------|---------------------------------|
| End point title        | Pharmacokinetic parameters (CL) |
| End point description: |                                 |

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Treatment            |           |

|                             |                   |  |  |  |
|-----------------------------|-------------------|--|--|--|
| <b>End point values</b>     | PM01183           |  |  |  |
| Subject group type          | Reporting group   |  |  |  |
| Number of subjects analysed | 44 <sup>[6]</sup> |  |  |  |
| Units: l/h                  |                   |  |  |  |
| median (standard deviation) |                   |  |  |  |
| Cycle 1                     | 12.5 (± 7)        |  |  |  |
| Cycle 2                     | 13.4 (± 8.2)      |  |  |  |

Notes:

[6] - Cycle 1: N=44

Cycle 2: N=33

|                                   |                                    |
|-----------------------------------|------------------------------------|
| <b>Attachments (see zip file)</b> | Total body clearance per cycle.bmp |
|-----------------------------------|------------------------------------|

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Overall period

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

### Dictionary used

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

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

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | PM01183 |
|-----------------------|---------|

Reporting group description:

PM01183 was given at a dose of 7.0 mg FD as a 1-hour q3wk i.v. infusion. Each cycle lasted three weeks.

| Serious adverse events                            | PM01183          |  |  |
|---------------------------------------------------|------------------|--|--|
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 32 / 44 (72.73%) |  |  |
| number of deaths (all causes)                     | 42               |  |  |
| number of deaths resulting from adverse events    | 3                |  |  |
| Investigations                                    |                  |  |  |
| Alanine aminotransferase increased                |                  |  |  |
| subjects affected / exposed                       | 1 / 44 (2.27%)   |  |  |
| occurrences causally related to treatment / all   | 3 / 3            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Aspartate aminotransferase increased              |                  |  |  |
| subjects affected / exposed                       | 1 / 44 (2.27%)   |  |  |
| occurrences causally related to treatment / all   | 3 / 3            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Blood bilirubin increased                         |                  |  |  |
| subjects affected / exposed                       | 2 / 44 (4.55%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 4            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Blood creatine increased                          |                  |  |  |
| subjects affected / exposed                       | 1 / 44 (2.27%)   |  |  |
| occurrences causally related to treatment / all   | 1 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |



|                                                                     |                  |  |  |
|---------------------------------------------------------------------|------------------|--|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |  |  |
| tumour associated fever                                             |                  |  |  |
| subjects affected / exposed                                         | 1 / 44 (2.27%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| tumour pain                                                         |                  |  |  |
| subjects affected / exposed                                         | 1 / 44 (2.27%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Vascular disorders                                                  |                  |  |  |
| Hypertensive crisis                                                 |                  |  |  |
| subjects affected / exposed                                         | 1 / 44 (2.27%)   |  |  |
| occurrences causally related to treatment / all                     | 0 / 1            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Blood and lymphatic system disorders                                |                  |  |  |
| Anaemia                                                             |                  |  |  |
| subjects affected / exposed                                         | 5 / 44 (11.36%)  |  |  |
| occurrences causally related to treatment / all                     | 5 / 6            |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Febrile neutropenia                                                 |                  |  |  |
| subjects affected / exposed                                         | 9 / 44 (20.45%)  |  |  |
| occurrences causally related to treatment / all                     | 11 / 11          |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| Neutropenia                                                         |                  |  |  |
| subjects affected / exposed                                         | 5 / 44 (11.36%)  |  |  |
| occurrences causally related to treatment / all                     | 6 / 6            |  |  |
| deaths causally related to treatment / all                          | 1 / 1            |  |  |
| Thrombocytopenia                                                    |                  |  |  |
| subjects affected / exposed                                         | 11 / 44 (25.00%) |  |  |
| occurrences causally related to treatment / all                     | 16 / 16          |  |  |
| deaths causally related to treatment / all                          | 0 / 0            |  |  |
| General disorders and administration site conditions                |                  |  |  |
| Fatigue                                                             |                  |  |  |

|                                                        |                 |  |  |
|--------------------------------------------------------|-----------------|--|--|
| subjects affected / exposed                            | 1 / 44 (2.27%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Gastrointestinal disorders</b>                      |                 |  |  |
| Abdominal pain                                         |                 |  |  |
| subjects affected / exposed                            | 2 / 44 (4.55%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Intestinal obstruction                                 |                 |  |  |
| subjects affected / exposed                            | 2 / 44 (4.55%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 3           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Nausea                                                 |                 |  |  |
| subjects affected / exposed                            | 2 / 44 (4.55%)  |  |  |
| occurrences causally related to treatment / all        | 1 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Rectal haemorrhage                                     |                 |  |  |
| subjects affected / exposed                            | 1 / 44 (2.27%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 1           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| Vomiting                                               |                 |  |  |
| subjects affected / exposed                            | 5 / 44 (11.36%) |  |  |
| occurrences causally related to treatment / all        | 2 / 5           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Hepatobiliary disorders</b>                         |                 |  |  |
| Cholangitis                                            |                 |  |  |
| subjects affected / exposed                            | 2 / 44 (4.55%)  |  |  |
| occurrences causally related to treatment / all        | 0 / 2           |  |  |
| deaths causally related to treatment / all             | 0 / 0           |  |  |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                 |  |  |
| haemoptysis                                            |                 |  |  |
| subjects affected / exposed                            | 1 / 44 (2.27%)  |  |  |
| occurrences causally related to treatment / all        | 1 / 1           |  |  |
| deaths causally related to treatment / all             | 1 / 1           |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| Pneumonitis                                     |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pneumothorax                                    |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Pulmonary embolism                              |                |  |  |
| subjects affected / exposed                     | 2 / 44 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal and urinary disorders                     |                |  |  |
| Acute prerenal failure                          |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Haematuria                                      |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Renal failure                                   |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |
| Renal failure acute                             |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Infections and infestations                     |                |  |  |
| Bacteraemia                                     |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |

|                                                 |                |  |  |  |
|-------------------------------------------------|----------------|--|--|--|
| Bronchopneumopathy                              |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Escherichia infection                           |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Escherichia sepsis                              |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Klebsiella bacteraemia                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Liver abscess                                   |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Neutropenic sepsis                              |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 1 / 1          |  |  |  |
| Pneumonia                                       |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Sepsis                                          |                |  |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |  |
| occurrences causally related to treatment / all | 1 / 1          |  |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |  |
| Septic shock                                    |                |  |  |  |

|                                                 |                |  |  |
|-------------------------------------------------|----------------|--|--|
| subjects affected / exposed                     | 2 / 44 (4.55%) |  |  |
| occurrences causally related to treatment / all | 0 / 2          |  |  |
| deaths causally related to treatment / all      | 0 / 0          |  |  |
| Metabolism and nutrition disorders              |                |  |  |
| Decreased appetite                              |                |  |  |
| subjects affected / exposed                     | 1 / 44 (2.27%) |  |  |
| 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 %

|                                                                     |                   |  |  |
|---------------------------------------------------------------------|-------------------|--|--|
| <b>Non-serious adverse events</b>                                   | PM01183           |  |  |
| Total subjects affected by non-serious adverse events               |                   |  |  |
| subjects affected / exposed                                         | 44 / 44 (100.00%) |  |  |
| Investigations                                                      |                   |  |  |
| Alanine aminotransferase increased                                  |                   |  |  |
| subjects affected / exposed                                         | 3 / 44 (6.82%)    |  |  |
| occurrences (all)                                                   | 3                 |  |  |
| Weight decreased                                                    |                   |  |  |
| subjects affected / exposed                                         | 8 / 44 (18.18%)   |  |  |
| occurrences (all)                                                   | 12                |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |  |  |
| Tumour pain                                                         |                   |  |  |
| subjects affected / exposed                                         | 23 / 44 (52.27%)  |  |  |
| occurrences (all)                                                   | 73                |  |  |
| Vascular disorders                                                  |                   |  |  |
| Hypertension                                                        |                   |  |  |
| subjects affected / exposed                                         | 3 / 44 (6.82%)    |  |  |
| occurrences (all)                                                   | 3                 |  |  |
| Phlebitis                                                           |                   |  |  |
| subjects affected / exposed                                         | 3 / 44 (6.82%)    |  |  |
| occurrences (all)                                                   | 6                 |  |  |
| Cardiac disorders                                                   |                   |  |  |
| Tachycardia                                                         |                   |  |  |
| subjects affected / exposed                                         | 4 / 44 (9.09%)    |  |  |
| occurrences (all)                                                   | 17                |  |  |

|                                                                                                                                                                                                                                                                     |                                                                                    |  |  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--|--|
| Nervous system disorders<br>Lethargy<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                            | 3 / 44 (6.82%)<br>9                                                                |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)              | 8 / 44 (18.18%)<br>14<br><br>12 / 44 (27.27%)<br>16<br><br>5 / 44 (11.36%)<br>5    |  |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 28 / 44 (63.64%)<br>118<br><br>7 / 44 (15.91%)<br>13<br><br>12 / 44 (27.27%)<br>14 |  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Ascites<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea        | 9 / 44 (20.45%)<br>19<br><br>3 / 44 (6.82%)<br>3<br><br>13 / 44 (29.55%)<br>20     |  |  |

|                                                 |                  |  |  |
|-------------------------------------------------|------------------|--|--|
| subjects affected / exposed                     | 14 / 44 (31.82%) |  |  |
| occurrences (all)                               | 40               |  |  |
| Nausea                                          |                  |  |  |
| subjects affected / exposed                     | 28 / 44 (63.64%) |  |  |
| occurrences (all)                               | 58               |  |  |
| Vomiting                                        |                  |  |  |
| subjects affected / exposed                     | 20 / 44 (45.45%) |  |  |
| occurrences (all)                               | 42               |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Cough                                           |                  |  |  |
| subjects affected / exposed                     | 3 / 44 (6.82%)   |  |  |
| occurrences (all)                               | 4                |  |  |
| Dyspnoea                                        |                  |  |  |
| subjects affected / exposed                     | 7 / 44 (15.91%)  |  |  |
| occurrences (all)                               | 8                |  |  |
| Hiccups                                         |                  |  |  |
| subjects affected / exposed                     | 4 / 44 (9.09%)   |  |  |
| occurrences (all)                               | 6                |  |  |
| Psychiatric disorders                           |                  |  |  |
| Depression                                      |                  |  |  |
| subjects affected / exposed                     | 4 / 44 (9.09%)   |  |  |
| occurrences (all)                               | 10               |  |  |
| Musculoskeletal and connective tissue disorders |                  |  |  |
| Back pain                                       |                  |  |  |
| subjects affected / exposed                     | 3 / 44 (6.82%)   |  |  |
| occurrences (all)                               | 6                |  |  |
| Metabolism and nutrition disorders              |                  |  |  |
| Decreased appetite                              |                  |  |  |
| subjects affected / exposed                     | 16 / 44 (36.36%) |  |  |
| occurrences (all)                               | 29               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 27 January 2011  | This protocol amendment included the following changes:<br>1. Included the collection of an additional blood sample from patients who consented to the PGx substudy, immediately before treatment with PM01183, to perform a gene expression profile (GEP) on purified circulating tumor cell (CTC)-enriched fractions.<br>2. Added contact information for the Central Laboratory for PGx Analyses.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 21 November 2011 | Included the following changes<br>1.Updated contact information for the Sponsor<br>2.Clarified: the protocol sections describing the laboratories for PGx tissue and blood sample processing and analysis and the inclusion criteria to allow the recruitment of patients who failed gemcitabine-containing adjuvant therapy within six months and with metastatic disease at study entry<br>3.Changed the inclusion criteria to set a maximum accepted age of 75 years-old, the inclusion criterion regarding bilirubin levels to require patients to have both total bilirubin $\leq$ 1.5xULN and direct bilirubin $\leq$ ULN and the inclusion criterion regarding albumin levels<br>4.Clarified the eligibility criteria to exclude patients with rapidly deteriorating pancreatic cancer and/or uncontrolled symptoms, and patients who require or carry external drainage catheters (which are associated with an increased risk of infection)<br>5.Updated the inclusion criteria to reflect that the period of time that female patients must avoid becoming pregnant after treatment discontinuation had decreased from six months to six weeks, following the finding that only untraceable levels of PM01183 remain after six weeks<br>6.Updated information on the authorized formulations of PM01183<br>7.Updated the hemoglobin value allowed for treatment continuation to make it consistent with the inclusion criteria<br>8.Increased the albumin value allowed for treatment continuation, due to the relevance of albumin levels as an independent prognostic factor in pancreatic cancer<br>9.Clarified the rules for replacing patients and for considering patients evaluable for efficacy<br>10.Changed the collection time of a blood sample for PGx analysis to "any time before the start of the second PM01183 infusion", as extending the collection period would help study logistics and treatment planning<br>11.Removed the description of the handling of PK samples in the protocol |

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported