Clinical trial results:
Phase II, Open-Label, Randomized, Controlled Study of PM060184 in Advanced, Hormone Receptor Positive, HER2 negative Breast Cancer Patients in Third or Fourth Line Setting.

Summary

EudraCT number	2015-002395-24
Trial protocol	ES BE
Global end of trial date	30 October 2017

Results information

Result version number	v1 (current)
This version publication date	16 November 2018
First version publication date	16 November 2018

Trial information

Trial identification

Sponsor protocol code	PM60184-B-001-15

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar, S.A.
Sponsor organisation address	Avenida de los Reyes, 1 Polígono Industrial "La Mina",, Colmenar Viejo, Madrid, Spain, 28770
Public contact	Clinical Development, Department of PharmaMar´s Oncology., Business Unit.,, 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	03 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2017
Global end of trial reached?	Yes
Global end of trial date	30 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To Evaluate the efficacy of PM060184 in terms of progression-free survival at 4 months (PFS4) in third or fourth line setting in the subset population of advanced, hormone receptor positive, human epidermal growth factor receptor 2 (HER2) negative, breast carcinoma

Protection of trial subjects:

The study was in compliance with ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy:

Primary antiemetic prophylaxis was compulsory prior to all PM060184 administrations. Standard treatment, according to ASCO guidelines, was administered:
- 5-HT3 antagonists (ondansetron 8 mg or equivalent).
- Steroids (dexamethasone 8 mg or equivalent).
- Both oral and i.v. formulations were allowed, following the local institutional standards.

If necessary, additional and/or extended antiemetic treatment could be considered (according to the Investigators' standard practice).

Evidence for comparator: -

Actual start date of recruitment	12 February 2016
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: 22
Worldwide total number of subjects	22
EEA total number of subjects	22

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)	18
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At cutoff date, 22 patients had been included in the 1st stage: 21 were treated and evaluable for safety, and 18 were evaluable for the primary efficacy endpoint (PFS4).
Patients enrollment between 12Feb2016 and 30Oct2017 (date of last F-Up, clinical cutoff) and corresponds to the 1st stage. All the patients were enrolled at 5 sites in Spain.

Pre-assignment

Screening details:

Screening details:
IC Signed,Age ≥18, Histologically diagnosis BC,Tumors HR+ & HER2-,2-3 chemotherapy lines,Previous treatment anthracyclines&taxanes,ECOG: PS 0 or 1,Adequate marrow,liver and kidney function, Normal LVEF by ECHO or MUGA,Life expectancy ≥ 3 mo.,Recovery grade≤1 from any toxicity,Peripheral neuropathy grade ≤ 1 for AE,negative pre

Period 1

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

Blinding implementation details:

Not blinded

Arms

Arm title	PM060184

Arm description:

The only drug administered and evaluated was PM060184, which was administered i.v. via a central line or a peripheral venous catheter (in 5 or 1-min administrations) at a dose of 9.3 mg/m2 on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle).

Arm type	Experimental
Investigational medicinal product name	PM060184
Investigational medicinal product code	PM060184
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

The only drug administered and evaluated was PM060184, which was administered i.v. via a central line or a peripheral venous catheter (in 5 or 1-min administrations) at a dose of 9.3 mg/m2 on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle).
The drug substance PM060184-CD is a mixture of PM060184 and 2-hydroxypropyl-β-cyclodextrin. PM060184 drug product (DP) is provided as a sterile lyophilized powder for concentrate for solution for infusion with a strength of 15 mg of the active moiety PM060184.
Before use, the vials should be reconstituted with 6 mL of water for injection to give a solution containing 2.5 mg/mL of PM060184. PM060184 as 15-mg DP was developed for i.v. administration. Prior to administration, the reconstituted vials were further diluted with a dextrose 5% solution for infusion. Each 15-mg vial of PM060184 was a single-use vial. The diluted solution should be protected from light exposure.

Number of subjects in period 1	PM060184
Started	22
Completed	0
Not completed	22
Clinical deterioration	1
Never treated	1
Progressive disease	12
Treatment-related adverse event	2
Patient refusal to treatment	6

Baseline characteristics

Reporting groups	
Reporting group title	PM060184
Reporting group description:	
The only drug administered and evaluated was PM060184, which was administered i.v. via a central line or a peripheral venous catheter (in 5 or 1-min administrations) at a dose of 9.3 mg/m2 on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle).	

Reporting group values	PM060184	Total	
Number of subjects	22	22	
Age categorical Units: Subjects			
18-49	11	11	
50-69	8	8	
≥70	3	3	
Age continuous Units: years			
median	51		
full range (min-max)	36 to 76	-	
Gender categorical Units: Subjects			
Female	22	22	
Male	0	0	
Race Units: Subjects			
White	21	21	
Other (Hispanic)	1	1	
ECOG PS Units: Subjects			
PS 0	11	11	
PS 1	11	11	
Stage at diagnosis Units: Subjects			
Stage I	1	1	
Stage IIA	8	8	
Stage IIB	2	2	
Stage IIIA	3	3	
Stage IIIC	2	2	
Stage IV	5	5	
Stage UK	1	1	
Primary tumor site Units: Subjects			
Bilateral	2	2	
Left	11	11	
Right	9	9	
Hystology type Units: Subjects			
Ductal	22	22	

Histology grade			
G: Grade			
Units: Subjects			
G1: Well differentiated	2	2	
G2: Moderately differentiated	16	16	
G3: Poorly differentiated	2	2	
G4: Undifferentiated	1	1	
GX: Grade cannot be assessed	1	1	
Second breast cancer Units: Subjects			
Yes	1	1	
No	21	21	
Hormone Receptor Units: Subjects			
Both hormone receptors positive	17	17	
Estrogen positive	5	5	
HER2 negative			
FISH: fluorescence in situ hybridization			
Units: Subjects			
HercepTest	15	15	
HercepTest and FISH	7	7	
Ki67/MIB-1 Units: Subjects			
<5%	2	2	
5-10%	1	1	
>10	13	13	
ND/UK	6	6	
BRCA status			
Patient had BRCA2 mutation and no sites of measurable disease reported in the source documents, but she was never treated with PM060184 and was excluded from the analysis of efficacy and safety.			
Units: Subjects			
No	3	3	
UK	18	18	
Yes	1	1	
Number of sites involved Units: Subjects			
0 site	1	1	
1 site	1	1	
2 sites	8	8	
3 sites	6	6	
4 sites	3	3	
5 sites	2	2	
6 sites	1	1	
Peripheral neuropathy Units: Subjects			
No	15	15	
Yes	7	7	
Type of peripheral neuropathy Units: Subjects			
Both (motor and sensory)	3	3	
Sensory	4	4	

No peripheral neuropathy	15	15	
NCI-CTCAE grade			
According to the NCI-CTCAE v.4.			
Units: Subjects			
Grade 1	4	4	
Grade 2	3	3	
No peripheral neuropathy	15	15	
Prior radiotherapy Units: Subjects			
Yes	16	16	
No	6	6	
Prior surgery for primary treatment Units: Subjects			
Mastectomy	11	11	
Breast-conserving surgery	8	8	
No surgery	3	3	
Number of prior lines Units: Subjects			
2 lines	2	2	
3 lines	3	3	
4 lines	4	4	
≥5 lines	13	13	
Number of prior lines for advanced/metastatic disease			
Includes chemotherapy and hormonotherapy.			
Units: Subjects			
2 lines	7	7	
3 lines	5	5	
≥5 lines	10	10	
Number of prior chemotherapy lines			
Includes neoadjuvant, adjuvant and advanced chemotherapy			
Units: Subjects			
2 lines	4	4	
3 lines	13	13	
4 lines	4	4	
5 lines	1	1	
Number of prior advanced chemotherapy lines Units: Subjects			
2 lines	14	14	
3 lines	8	8	
Best response to last prior therapy			
NE, not evaluable; PD, disease progression; PR, partial response; SD, stable disease; UK, unknown			
Units: Subjects			
PR	4	4	
SD	11	11	
PD	4	4	
UK/NE	3	3	
Weight Units: Kg			
median	63.7		
full range (min-max)	48 to 109.5	-	

Height			
Units: cm			
median	160		
full range (min-max)	151 to 168	-	
BSA			
BSA: Body Surface Area			
Units: m2			
median	1.6		
full range (min-max)	1.6 to 2.2	-	
Time from first diagnosis to first PM060184 infusion			
Data on 21 patients (one patient was never treated with PM060184)			
Units: months			
median	108.7		
full range (min-max)	14.3 to 416.5	-	
Time from first diagnosis of advance disease to first PM060184 infusion			
Data on 21 patients (one patient was never treated with PM060184)			
Units: months			
median	35.4		
full range (min-max)	11.8 to 132.8	-	
Time from prior last progression before study entry			
Patient signed informed consent on 20 September 2016. Although suspicion of disease progression was previous (20 August 2016), PD was confirmed through CT scan on 28 September 2016 and PM060184 treatment was started on 29 September 2016.			
Units: months			
median	0.4		
full range (min-max)	-0.3 to 1.5	-	
Time from stop date of last prior therapy to study entry			
Units: months			
median	0.7		
full range (min-max)	0.2 to 2.4	-	
Number of sites involved			
Units: Sites			
median	3		
full range (min-max)	0 to 6	-	
Number of prior lines			
Units: Lines			
median	5		
full range (min-max)	2 to 8	-	
Number of prior lines for advanced/metastatic disease			
Includes neoadjuvant, adjuvant and advanced chemotherapy			
Units: Lines			
median	3		
full range (min-max)	2 to 7	-	
Number of prior chemotherapy lines			
Includes neoadjuvant, adjuvant and advanced chemotherapy			
Units: Lines			
median	3		
full range (min-max)	2 to 5	-	
Number of prior advanced			

chemotherapy lines			
Units: lines			
median	2		
full range (min-max)	2 to 3	-	
Progression-free interval			
Units: months			
median	0.4		
full range (min-max)	-0.3 to 1.5	-	

End points

End points reporting groups

Reporting group title	PM060184

Reporting group description:

The only drug administered and evaluated was PM060184, which was administered i.v. via a central line or a peripheral venous catheter (in 5 or 1-min administrations) at a dose of 9.3 mg/m2 on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle).

Primary: Progression-free survival rate at four months (PFS4)

End point title	Progression-free survival rate at four months (PFS4)[1]

End point description:

Progression-free survival rate at four months (PFS4), defined as the rate estimate of the percentage of patients who were alive and progression-free at 16 weeks (~4 months) after the first treatment administration.

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: The threshold for proving antitumor activity (at least nine patients reaching PFS4) was not reached, the primary endpoint was unmet, and the study was closed without recruiting more patients in the first stage and without opening the second stage.

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	18[2]			
Units: percentage				
number (confidence interval 95%)				
Yes	11.1 (1.4 to 34.7)			
No	88.9 (65.3 to 98.6)			

Notes:

[2] - Four patients were not considered evaluable for efficacy

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

OS, defined as the time from the first day of treatment to the date of death or last contact.

End point type	Secondary

End point timeframe:

Overall period

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	18[3]			
Units: months				
median (confidence interval 95%)	6.6 (4.5 to 999)			

Notes:

[3] - Four patients were not considered evaluable for efficacy
999= not reached

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival

End point description:

PFS, defined as the time from the first day of study treatment to the day of negative efficacy assessment (progression or death) or last tumor evaluation

PFS at 6 months (95% CI): 9.7% (0-27.4)

End point type	Secondary

End point timeframe:

Overall period

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	18[4]			
Units: months				
median (confidence interval 95%)	1.9 (1.2 to 3.8)			

Notes:

[4] - Four patients were not considered evaluable for efficacy

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

ORR, defined as the percentage of patients with objective response, either CR or PR according to the RECIST v.1.1 criteria
CR, complete response; ORR, overall response rate; PD, disease progression; PR, partial response; SD, stable disease.

ORR (95% CI) 5.6% (0.1-27.3%)
Clinical benefit rate (CR+PR+SD ≥ 4 months) (95% CI) 16.7% (3.6-41.4%)

Only one patient achieved a partial response, which lasted 1.9 months

End point type	Secondary

End point timeframe:

Overall period

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	18[5]			
Units: subjects				
PR	1			
SD	8			
PD	9			

Notes:

[5] - Four patients were not considered evaluable for efficacy'

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	18.0

Reporting groups	
Reporting group title	PM060184

Reporting group description: -

Serious adverse events	PM060184		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 21 (19.05%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Wrist surgery			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	PM060184		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 21 (100.00%)		
Investigations			
Alt increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Ast increased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	4		
Weight decreased			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	3		
Nervous system disorders			
Neuropathy peripheral			
subjects affected / exposed	9 / 21 (42.86%)		
occurrences (all)	39		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	4		
Thrombocytopenia			
subjects affected / exposed	3 / 21 (14.29%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 21 (85.71%)		
occurrences (all)	59		
Pyrexia			
subjects affected / exposed	5 / 21 (23.81%)		
occurrences (all)	5		
Gastrointestinal disorders			

Abdominal distension subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Abdominal pain subjects affected / exposed occurrences (all)	11 / 21 (52.38%) 24		
Constipation subjects affected / exposed occurrences (all)	5 / 21 (23.81%) 9		
Diarrhoea subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 13		
Nausea subjects affected / exposed occurrences (all)	13 / 21 (61.90%) 23		
Vomiting subjects affected / exposed occurrences (all)	6 / 21 (28.57%) 9		
Respiratory, thoracic and mediastinal disorders			
Cough subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3		
Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 14		
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	4 / 21 (19.05%) 5		
Back pain subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 6		

Bone pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 4 5 / 21 (23.81%) 11		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) Hypophosphataemia subjects affected / exposed occurrences (all)	8 / 21 (38.10%) 20 2 / 21 (9.52%) 3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The threshold for proving antitumor activity (at least nine patients reaching PFS4) was not reached, the primary endpoint was unmet, and the study was closed without recruiting more patients in the first stage and without opening the second stage

Notes: