



Clinical trial results:

A Phase II, Open-label, Multicenter Study of PM060184 in Patients with Advanced Colorectal Cancer after Standard Treatment

Summary

EudraCT number	2017-000257-39
Trial protocol	ES
Global end of trial date	11 February 2019

Results information

Result version number	v1 (current)
This version publication date	31 October 2020
First version publication date	31 October 2020

Trial information

Trial identification

Sponsor protocol code	PM60184-B-002-17
-----------------------	------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03427268
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pharma Mar, S.A.
Sponsor organisation address	Avenida de los Reyes, 1 Polígono Industrial "La Mina", Colmenar Viejo, Madrid, Spain, 28770
Public contact	Clinical Development, Department of PharmaMar's Oncology, Business Unit., Pharmamar, S.A., 34 91846 60 00, clinicaltrials@pharmamar.com
Scientific contact	Clinical Development, Department of PharmaMar's Oncology, Business Unit., Pharmamar, 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 August 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2019
Global end of trial reached?	Yes
Global end of trial date	11 February 2019
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 12 weeks (PFS3) in patients with advanced colorectal carcinoma (CRC) after standard therapy.

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 American Society of Clinical Oncology (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 in accordance with ASCO guidelines

Evidence for comparator: -

Actual start date of recruitment	16 January 2018
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: 31
Country: Number of subjects enrolled	Canada: 1
Worldwide total number of subjects	32
EEA total number of subjects	31

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)	23
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first informed consent was signed on 16 January 2018 and the first study treatment administration was on 8 February 2018. The cutoff date for the results was 11 February 2019 (date of last follow-up).

Pre-assignment

Screening details:

signed CI; Age ≥ 18 years; Histologically-citologically documented adenocarcinoma of colon or rectum that had progressed to the last prior treatment before inclusion; Measurable disease according to RECIST v.1.1; Previous treatment in any setting with fluoropyrimidine, oxaliplatin and irinotecan in any combination; No more than 2 previous therapies

Period 1

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

Arms

Arm title	PM060184
-----------	----------

Arm description:

PM060184 was administered i.v. via a central line or a peripheral venous catheter (in 30-min administration) at a dose of 9.3 mg/m² on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle) (dose can be rounded to the first decimal point).

Arm type	Experimental
Investigational medicinal product name	PM060184
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PM060184 was administered i.v. via a central line or a peripheral venous catheter (in 30-min administration) at a dose of 9.3 mg/m² on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle) (dose can be rounded to the first decimal point).

Number of subjects in period 1	PM060184
Started	32
Completed	0
Not completed	32
Consent withdrawn by subject	1
Study termination	1
Never treated	2
Progressive disease	25
Treatment-related adverse event	3

Baseline characteristics

Reporting groups

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

Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	32	32	
Age categorical			
Units: Subjects			
18-49	4	4	
50-69	23	23	
≥70	5	5	
Age continuous			
Units: years			
median	62		
full range (min-max)	36 to 74	-	
Gender categorical			
Units: Subjects			
Female	17	17	
Male	15	15	
Race			
Units: Subjects			
White	32	32	
ECOG PS			
ECOG PS, Eastern Cooperative Oncology Group performance status			
Units: Subjects			
PS 0	15	15	
PS I	17	17	
Stage at diagnosis			
Units: Subjects			
Stage I	1	1	
Stage IIIB	5	5	
Stage IIIC	2	2	
Stage IV	17	17	
Stage IVA	3	3	
Stage IVB	3	3	
UK	1	1	
Primary tumor side			
Units: Subjects			
Left	22	22	
Right	10	10	
Histology grade			
Units: Subjects			
G1: Well differentiated	8	8	
G2: Moderately differentiated	18	18	
G4: Undifferentiated	1	1	
GX: Grade cannot be assessed	5	5	

KRAS mutation status			
Units: Subjects			
Mutated	25	25	
Not done	6	6	
UK	1	1	
Sites involved			
Units: Subjects			
1 site	5	5	
2 sites	12	12	
3 sites	8	8	
4 sites	5	5	
6 sites	1	1	
7 sites	1	1	
Peripheral neuropathy			
Units: Subjects			
Yes	19	19	
No	13	13	
Prior surgery			
Units: Subjects			
Yes	28	28	
No	4	4	
Prior radiotherapy			
Units: Subjects			
Concurrent	1	1	
Palliative	4	4	
No	27	27	
Prior anticancer lines			
Units: Subjects			
1 line	1	1	
2 lines	26	26	
3 lines	5	5	
Best response to last prior therapy			
CR, complete response; PD, disease progression; PR, partial response; SD, stable disease; UK,unknown			
Units: Subjects			
CR	2	2	
PR	3	3	
SD	14	14	
PD	9	9	
UK	4	4	
Weight			
Units: Kg			
median	67		
full range (min-max)	39.6 to 105.5	-	
Height			
Units: cm			
median	166		
full range (min-max)	150 to 183	-	
Body surface area			
Units: m^2			
median	1.8		
full range (min-max)	1.3 to 2.3	-	

Time from diagnosis of advanced disease to study entry Units: months median full range (min-max)	17.3 5.8 to 69.5	-	
Time from first diagnosis to first PM060184 infusion Units: months median full range (min-max)	22.9 7.9 to 57.1	-	
Time from prior last progression before study entry Units: months median full range (min-max)	1.2 0 to 3.2	-	
Time from stop date of prior chemotherapy to study entry Units: months median full range (min-max)	1.8 0.1 to 6.3	-	
Sites involved Units: sites median full range (min-max)	2 1 to 7	-	
Prior anticancer lines Units: lines median full range (min-max)	2 1 to 3	-	

End points

End points reporting groups

Reporting group title	PM060184
Reporting group description: PM060184 was administered i.v. via a central line or a peripheral venous catheter (in 30-min administration) at a dose of 9.3 mg/m ² on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle) (dose can be rounded to the first decimal point).	

Primary: Progression-free survival rate at three months

End point title	Progression-free survival rate at three months ^[1]
End point description: Progression-free survival rate at 12 weeks (PFS3), defined as the rate estimate of the percentage of patients who are alive and progression-free at 12 weeks (~3 months) after the first treatment administration.	
End point type	Primary
End point timeframe: Time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation, up to 3 months	
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 exact binomial estimator and its 95% confidence interval (CI) were used for the primary endpoint (PFS3)	

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	29 ^[2]			
Units: percentage of participants				
number (confidence interval 95%)	20.7 (8 to 39.7)			

Notes:
[2] - 2 patients were never treated
1 treated patient not receive 2 administrations over 2 cycles

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
End point description: Events 15 (51.7%) 999, not reached	
End point type	Secondary
End point timeframe: From the first day of treatment to the date of death or last contact	

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	29 ^[3]			
Units: months				
median (confidence interval 95%)	9.8 (4.6 to 999)			

Notes:

[3] - 2 patients were never treated

1 treated patient not receive 2 administrations over 2 cycles

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival

End point title	Progression-free Survival
-----------------	---------------------------

End point description:

Progression-free survival (PFS), defined as the time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation

End point type	Secondary
----------------	-----------

End point timeframe:

Time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	29 ^[4]			
Units: months				
median (confidence interval 95%)	2.6 (1.3 to 2.8)			

Notes:

[4] - 2 patients were never treated

1 treated patient not receive 2 administrations over 2 cycles

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival at 3 months

End point title	Progression-free Survival at 3 months
-----------------	---------------------------------------

End point description:

Progression-free survival (PFS), defined as the time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation

End point type	Secondary
----------------	-----------

End point timeframe:

Time from the first day of study treatment to the day of assessment of progression, death or last tumor evaluation, up to 3 months

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	29 ^[5]			
Units: percentage of participants				
number (confidence interval 95%)	25.3 (9.1 to 41.4)			

Notes:

[5] - 2 patients were never treated

1 treated patient not receive 2 administrations over 2 cycles

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate
-----------------	-----------------------

End point description:

Overall Response Rate defined as the percentage of patients with either complete response (CR) or partial response (PR) according to RECIST v.1.1.

PD, disease progression; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors

End point type	Secondary
----------------	-----------

End point timeframe:

Overall period

End point values	PM060184			
Subject group type	Reporting group			
Number of subjects analysed	29 ^[6]			
Units: subjects				
SD <3 months	9			
SD ≥3 months	7			
PD	13			

Notes:

[6] - 2 patients were never treated

1 treated patient not receive 2 administrations over 2 cycles

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	20.0
--------------------	------

Reporting groups

Reporting group title	PM060184
-----------------------	----------

Reporting group description:

PM060184 was administered i.v. via a central line or a peripheral venous catheter (in 30-min administration) at a dose of 9.3 mg/m² on Day 1 and Day 8 every three weeks (q3wk) (three weeks = one treatment cycle) (dose can be rounded to the first decimal point).

Serious adverse events	PM060184		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 30 (20.00%)		
number of deaths (all causes)	16		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Blood bilirubin increased			
subjects affected / exposed	1 / 30 (3.33%)		
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 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia pneumococcal			
subjects affected / exposed	1 / 30 (3.33%)		
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	PM060184		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 30 (100.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Aspartate aminotransferase increased			

subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Blood bilirubin increased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	5		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Weight decreased			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	7		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	7		
Hypertension			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	9		
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	10		
Dysgeusia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	4		
Hypoaesthesia			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	9		
Neurotoxicity			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	7		
Paraesthesia			

<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Peripheral sensory neuropathy</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>14 / 30 (46.67%)</p> <p>52</p> <p>3 / 30 (10.00%)</p> <p>12</p>		
<p>Blood and lymphatic system disorders</p> <p>Anaemia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 30 (23.33%)</p> <p>14</p> <p>3 / 30 (10.00%)</p> <p>3</p>		
<p>General disorders and administration site conditions</p> <p>Asthenia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Chest pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Pyrexia</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>22 / 30 (73.33%)</p> <p>74</p> <p>2 / 30 (6.67%)</p> <p>4</p> <p>5 / 30 (16.67%)</p> <p>10</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal distension</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Constipation</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Diarrhoea</p>	<p>2 / 30 (6.67%)</p> <p>2</p> <p>20 / 30 (66.67%)</p> <p>66</p> <p>5 / 30 (16.67%)</p> <p>15</p> <p>19 / 30 (63.33%)</p> <p>61</p>		

subjects affected / exposed	11 / 30 (36.67%)		
occurrences (all)	33		
Nausea			
subjects affected / exposed	9 / 30 (30.00%)		
occurrences (all)	23		
Vomiting			
subjects affected / exposed	4 / 30 (13.33%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	14 / 30 (46.67%)		
occurrences (all)	54		
Pruritus			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	11		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	7		
Insomnia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	9		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 30 (16.67%)		
occurrences (all)	13		
Musculoskeletal chest pain			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	6		
Infections and infestations			
Device related infection			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	10 / 30 (33.33%)		
occurrences (all)	26		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 July 2017	<p>The main objective of this amendment was to change the infusion time of PM060184 from 1 minute to 30 minutes. This was decided following the analysis of preliminary data from the phase II trial PM60184-B-001-15 in hormone receptor-positive, HER2-negative, advanced breast cancer patients, which evaluated short infusion times (one and five minutes) to simplify PM060184 administration. Preliminary safety data from this trial suggest that the overall toxicity profile of PM060184 administered at shorter infusion times (one minute and five minutes) was similar to that observed in 104 patients treated with single-agent PM060184 at different doses during phase I trials. However, it seems that the higher maximum plasma concentration (C_{max}) of shorter infusion times was associated with an increased incidence of adverse events at the dose of 9.3 mg/m². In addition, results from the phase I trial PM60184-A-002a-10, which evaluated the same schedule but at an infusion of 10 minutes, showed that at the recommended dose (RD) of 9.3 mg/m² five patients had Day 8 infusion omissions, but in only one case the omission was due to drug-related toxicity (grade 2 neutropenia). Thus, the relative dose intensity was 91.3%. Furthermore, due to its limited solubility, PM060184 must be administered in a very low volume by means of a syringe pump. This device's performance is highly affected by the system's pressure, which in turn depends on the duration of the infusion. Thus, the longer the infusion, the fewer chances of device malfunction. Besides, longer infusion times are more convenient for reliable characterization of pharmacokinetic (PK) parameters, especially maximum plasma concentration (C_{max}), since these parameters are not affected by variability at the collection window around the end of infusion as much as in shorter infusions. In accordance with these considerations, the infusion time of PM060184 was changed to 30 minutes and the reconstitution guidelines were updated.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported