Clinical trial results:
A randomized, multicenter, open-label, phase II trial to evaluate the efficacy and safety of palbociclib in combination with fulvestrant or letrozole in patients with HER2 negative, ER+ metastatic breast cancer.

Summary

EudraCT number	2014-004698-17
Trial protocol	ES GB IT DE CZ
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	12 March 2022
First version publication date	12 March 2022
Summary attachment (see zip file)	PARSIFAL clinical study report (Abbreviated_Clinical study report_PARSIFAL_01-10-2020_MedSIR.docx)

Trial information

Trial identification

Sponsor protocol code	MedOPP067

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02491983
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medica Scientia Innovation Research (MedSIR)
Sponsor organisation address	Av Diagonal 211, Torre Glories - 27th floor, Barcelona, Spain, 08018
Public contact	Sr Global Project Manager, Medica Scientia Innovation Research (MedSIR), +34 932 214 135, alicia.garcia@medsir.org
Scientific contact	Sr Global Project Manager, Medica Scientia Innovation Research (MedSIR), +34 932 214 135, alicia.garcia@medsir.org

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	01 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2020
Global end of trial reached?	Yes
Global end of trial date	31 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of the combination of palbociclib plus fulvestrant or palbociclib plus letrozole in terms of 1-year progression-free survival (PFS) in patients with hormone-sensitive HER2-negative metastatic or locally advanced breast cancer

Protection of trial subjects:

Study progress will be monitored by MedSIR or its representative (e.g., a CRO) as frequently as necessary to ensure:
That the rights and well-being of human subjects are protected;
- the reported trial data are accurate, complete, and verifiable from the source documents; and
- the conduct of the trial is in compliance with the current approved protocol/amendment(s), GCP, and applicable regulatory requirements.

Background therapy:

Palbociclib (PD-0332991) is an oral and selective inhibitor of cyclin dependent kinases 4 and 6 (CDK4/6) with little or no activity against a large panel of 274 other protein kinases. The only known natural substrate for Cdk4/cyclin D1 is the retinoblastoma gene product, Rb. Palbociclib has shown to have no effect in Rb-negative tumor cells.

Letrozole (Femara®) is an oral non-steroidal aromatase inhibitor and it is approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (ABC).

Fulvestrant is a novel estrogen-receptor antagonist that, unlike Tamoxifen, is devoid of any agonist activity. After binding to the ER, Fulvestrant induces a rapid degradation and loss of ER and the PgR. As a result, there is less chance of the estrogen receptor being activated by alternative pathways that are believed to cause resistance.

Evidence for comparator: -	
Actual start date of recruitment	17 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 255
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	Czechia: 14
Country: Number of subjects enrolled	France: 70
Country: Number of subjects enrolled	Germany: 24
Country: Number of subjects enrolled	Italy: 38

Country: Number of subjects enrolled	Russian Federation: 31
Worldwide total number of subjects	486
EEA total number of subjects	401

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)	273
From 65 to 84 years	209
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Postmenopausal women and premenopausal women receiving LHRH analogues, aged ≥ 18 years with ER positive and HER2 negative locally advanced or metastatic breast cancer that had not received any therapy for the metastatic disease.

Pre-assignment

Screening details:

- Postmenopausal and premenopausal women receiving LHRH analogues, ≥ 18 years.
- ECOG score ≤ 2
- Histologically confirmed ER+ and/or PgR+ and HER2- locally advanced or MBC
- Not candidates for a local treatment with a radical intention
- No prior therapy for metastatic disease.
- Evidence of measurable or evaluable metastatic disease

Pre-assignment period milestones

Number of subjects started	486
Number of subjects completed	486

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Palbociclib + Fulvestrant

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

Fulvestrant will be supplied as two pre-filled syringe (5 ml) that contains each one 250 mg fulvestrant and other ingredients (excipients) like ethanol (96 per cent), benzyl alcohol, benzyl benzoate and castor oil. Fulvestrant is a clear, colourless to yellow, viscous solution in a pre-filled syringe fitted with a tamper-evident closure, containing 5 ml solution for injection. Two syringes must be administered to receive the 500 mg recommended monthly dose.

Investigational medicinal product name	Pablociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib (PD-0332991) will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of PD-0332991 free base. The sponsor will supply the oral drug formulation to sites in HDPE (High-density polyethylene) bottles containing 75 mg, 100mg, or 125 mg capsules. The capsules can be differentiated by their size and colour.

Arm title	Palbociclib + Letrozole

Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib (PD-0332991) will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of PD-0332991 free base. The sponsor will supply the oral drug formulation to sites in HDPE (High-density polyethylene) bottles containing 75 mg, 100mg, or 125 mg capsules. The capsules can be differentiated by their size and colour.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole: Commercially available letrozole 2.5 mg film-coated tablets will be used in the study.

Number of subjects in period 1	Palbociclib + Fulvestrant	Palbociclib + Letrozole
Started	243	243
Completed	241	242
Not completed	2	1
Physician decision	1	-
Consent withdrawn by subject	-	1
Not meet selection criteria	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Palbociclib + Fulvestrant
Reporting group description: -	
Reporting group title	Palbociclib + Letrozole
Reporting group description: -	

Reporting group values	Palbociclib + Fulvestrant	Palbociclib + Letrozole	Total
Number of subjects	243	243	486
Age categorical Units: Subjects			
Adults (18-64 years)	131	142	273
From 65-84 years	111	98	209
85 years and over	1	3	4
Gender categorical Units: Subjects			
Female	243	243	486
Male	0	0	0

Subject analysis sets	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: Considering all patients included regardless of whether they received the required study drug exposure and protocol processing	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: Considering all patients that receive at least one drug exposure.	

Reporting group values	ITT	Safety	
Number of subjects	486	483	
Age categorical Units: Subjects			
Adults (18-64 years)	273	272	
From 65-84 years	209	207	
85 years and over	4	4	
Gender categorical Units: Subjects			
Female	486	483	
Male	0	0	

End points

End points reporting groups

Reporting group title	Palbociclib + Fulvestrant
Reporting group description: -	
Reporting group title	Palbociclib + Letrozole
Reporting group description: -	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Considering all patients included regardless of whether they received the required study drug exposure and protocol processing	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Considering all patients that receive at least one drug exposure.	

Primary: PFS

End point title	PFS
End point description:	
The progression-free survival will be compared between the two groups using a two-sided stratified log-rank test with site of disease (visceral vs. non-visceral) and by the onset of metastatic disease diagnose (de novo metastatic vs. non de novo patients) as strata. We will test the primary endpoint at a nominal levels of 0.001 and 0.0498 at interim and final analysis, respectively.	
End point type	Primary
End point timeframe:	
To evaluate the progression-free survival. This is defined as the time from randomization until objective tumor progression or death by any cause.	

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: PFS	243	243		

Statistical analyses

Statistical analysis title	PFS (per investigator's assessment)
Comparison groups	Palbociclib + Fulvestrant v Palbociclib + Letrozole
Number of subjects included in analysis	486
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.41

Secondary: Safety

End point title	Safety

End point description:

Analysis of safety-related data will be considered at four levels:
• First, the extent of exposure (dose, duration, number of patients) will be examined to determine the degree to which safety can be assessed from the study.
• Second, we will describe and compare clinically relevant test, concomitant medications and adverse events reported in every study group. For adverse events, we will report intensity, causality, body system, action taken, and outcome.
• Third, serious adverse events, deaths and study discontinuations will be described and examined in every study group.
• Finally, patient grade 3 and 4 toxicities in every study group will be classified by MedDRA system organ class and compared between patient baseline characteristics.
The relation between baseline characteristics and severe adverse events (classified in MedDRA SOCs) will be analyzed with chi-squared test followed by multivariate logistic regression with appropriate interaction terms.

End point type	Secondary

End point timeframe:

Patient safety and adverse events will be assessed using the CTCAE. Grade 3 and 4 adverse events and serious adverse events will be assessed to determine the safe and tolerability of the different drug combinations.

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: AESIs and SAEs	241	242		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to progression

End point title	Time to progression

End point description:

Secondary objective to compare the time to progression (TTP) of the combination of palbociclib plus fulvestrant with palbociclib plus letrozole.

End point type	Secondary

End point timeframe:

TTP is defined as the time from randomization to disease progression, as assessed by the investigator per RECIST v1.1

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: TTP	243	243		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Compare the overall survival (OS) of the combination of palbociclib plus fulvestrant with palbociclib plus letrozole.

End point type	Secondary

End point timeframe:

Overall survival is defined as the time from randomization until death from any cause

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: OS	243	243		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response

End point title	Overall response

End point description:

Secondary objective to compare the clinical response (in terms of clinical benefit and overall response) of the combination of palbociclib plus fulvestrant with palbociclib plus letrozole.

End point type	Secondary

End point timeframe:

The ORR is defined as the proportion of patients with best overall response of confirmed complete response (CR) or partial response (PR) based on local investigator’s assessment according to RECIST criteria guidelines (version 1.1).

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: ORR	243	243		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

End point title	Duration of response

End point description:

Secondary objective to compare the duration of response (DoR) of the combination of palbociclib plus fulvestrant with palbociclib plus letrozole.

End point type	Secondary

End point timeframe:

DoR is defined as the time from documentation of tumor response (either CR or PR) to disease progression. An objective response needs to be confirmed at least 4 weeks after the initial response

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: DoR	243	243		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response

End point title	Time to response

End point description:

Secondary objective to compare time to response (TTR) of the combination of palbociclib plus fulvestrant with palbociclib plus letrozole.

End point type	Secondary

End point timeframe:

TTR is defined as the time from randomization to the first overall tumor response (tumor shrinkage of ≥30%) observed for patients who achieved a CR or PR.

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: TTR	243	243		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate

End point title	Clinical benefit rate

End point description:

Secondary objective to compare the clinical response (in terms of clinical benefit and overall response) of the combination of palbociclib plus fulvestrant with palbociclib plus letrozole.

End point type	Secondary

End point timeframe:

The CBR is defined as the percentage of patients who experience a CR, PR or stable disease for at least 24 weeks and assessed by modified Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) criteria.

End point values	Palbociclib + Fulvestrant	Palbociclib + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243	243		
Units: CBR	243	243		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until 30 days after last study treatment dose

Adverse event reporting additional description:

All study patients will be carefully monitored for the occurrence of AEs (including SAEs and AESIs) during the above specified adverse event reporting period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20

Reporting groups

Reporting group title	Experimental arm

Reporting group description: -

Serious adverse events	Experimental arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 486 (5.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanina aminotransferasa increased			
subjects affected / exposed	4 / 486 (0.82%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferasa increased			
subjects affected / exposed	2 / 486 (0.41%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia			

subjects affected / exposed	1 / 486 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	1 / 486 (0.21%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Anaemia				
subjects affected / exposed	4 / 486 (0.82%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	3 / 486 (0.62%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile Neutropenia				
subjects affected / exposed	1 / 486 (0.21%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
subjects affected / exposed	1 / 486 (0.21%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 486 (0.21%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Diarrohea				
subjects affected / exposed	1 / 486 (0.21%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			

Stomatitis			
subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	3 / 486 (0.62%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	2 / 486 (0.41%)		
occurrences causally related to treatment / all	8 / 8		
deaths causally related to treatment / all	0 / 0		
Cough			
subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Hallucinations, mixed			
subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 486 (0.41%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 486 (0.21%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 486 (0.21%)		
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	Experimental arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	455 / 486 (93.62%)		
Vascular disorders			
Hot flush			
subjects affected / exposed	87 / 486 (17.90%)		
occurrences (all)	111		
Hypertension			
subjects affected / exposed	23 / 486 (4.73%)		
occurrences (all)	43		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	177 / 486 (36.42%)		
occurrences (all)	399		
Fatigue			

subjects affected / exposed	125 / 486 (25.72%)		
occurrences (all)	264		
Pyrexia			
subjects affected / exposed	47 / 486 (9.67%)		
occurrences (all)	57		
Oedema peripheral			
subjects affected / exposed	40 / 486 (8.23%)		
occurrences (all)	49		
Pain			
subjects affected / exposed	30 / 486 (6.17%)		
occurrences (all)	34		
Injection site pain			
subjects affected / exposed	15 / 486 (3.09%)		
occurrences (all)	16		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	96 / 486 (19.75%)		
occurrences (all)	139		
Dyspnoea			
subjects affected / exposed	62 / 486 (12.76%)		
occurrences (all)	88		
Epistaxis			
subjects affected / exposed	33 / 486 (6.79%)		
occurrences (all)	49		
Pulmonary embolism			
subjects affected / exposed	18 / 486 (3.70%)		
occurrences (all)	18		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	39 / 486 (8.02%)		
occurrences (all)	46		
Anxiety			
subjects affected / exposed	30 / 486 (6.17%)		
occurrences (all)	36		
Depression			

subjects affected / exposed	25 / 486 (5.14%)		
occurrences (all)	31		
Investigations			
Alanine aminotransferasa increased			
subjects affected / exposed	29 / 486 (5.97%)		
occurrences (all)	48		
Aspartate aminotransferasa increased			
subjects affected / exposed	28 / 486 (5.76%)		
occurrences (all)	45		
Nervous system disorders			
Headache			
subjects affected / exposed	67 / 486 (13.79%)		
occurrences (all)	113		
Dizziness			
subjects affected / exposed	36 / 486 (7.41%)		
occurrences (all)	48		
Paraesthesia			
subjects affected / exposed	31 / 486 (6.38%)		
occurrences (all)	41		
Dysgeusia			
subjects affected / exposed	29 / 486 (5.97%)		
occurrences (all)	34		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	405 / 486 (83.33%)		
occurrences (all)	3939		
Anaemia			
subjects affected / exposed	123 / 486 (25.31%)		
occurrences (all)	323		
Leukopenia			
subjects affected / exposed	121 / 486 (24.90%)		
occurrences (all)	771		
Thrombocytopenia			
subjects affected / exposed	88 / 486 (18.11%)		
occurrences (all)	216		
Lymphopenia			

subjects affected / exposed	36 / 486 (7.41%)		
occurrences (all)	88		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	23 / 486 (4.73%)		
occurrences (all)	30		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	125 / 486 (25.72%)		
occurrences (all)	200		
Nausea			
subjects affected / exposed	102 / 486 (20.99%)		
occurrences (all)	128		
Stomatitis			
subjects affected / exposed	88 / 486 (18.11%)		
occurrences (all)	193		
Constipation			
subjects affected / exposed	74 / 486 (15.23%)		
occurrences (all)	112		
Vomiting			
subjects affected / exposed	74 / 486 (15.23%)		
occurrences (all)	114		
Abdominal pain upper			
subjects affected / exposed	53 / 486 (10.91%)		
occurrences (all)	75		
Dyspepsia			
subjects affected / exposed	46 / 486 (9.47%)		
occurrences (all)	61		
Dry mouth			
subjects affected / exposed	21 / 486 (4.32%)		
occurrences (all)	21		
Toothache			
subjects affected / exposed	19 / 486 (3.91%)		
occurrences (all)	25		
Haemorrhoids			

subjects affected / exposed	17 / 486 (3.50%)		
occurrences (all)	18		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	117 / 486 (24.07%)		
occurrences (all)	135		
Pruritus			
subjects affected / exposed	53 / 486 (10.91%)		
occurrences (all)	75		
Rash			
subjects affected / exposed	41 / 486 (8.44%)		
occurrences (all)	48		
Dry skin			
subjects affected / exposed	28 / 486 (5.76%)		
occurrences (all)	34		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	142 / 486 (29.22%)		
occurrences (all)	240		
Back pain			
subjects affected / exposed	106 / 486 (21.81%)		
occurrences (all)	173		
Pain in extremity			
subjects affected / exposed	67 / 486 (13.79%)		
occurrences (all)	83		
Musculoskeletal pain			
subjects affected / exposed	50 / 486 (10.29%)		
occurrences (all)	67		
Bone pain			
subjects affected / exposed	43 / 486 (8.85%)		
occurrences (all)	58		
Musculoskeletal chest pain			
subjects affected / exposed	28 / 486 (5.76%)		
occurrences (all)	34		
Muscle spasm			

subjects affected / exposed	27 / 486 (5.56%)		
occurrences (all)	39		
Myalgia			
subjects affected / exposed	23 / 486 (4.73%)		
occurrences (all)	33		
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	64 / 486 (13.17%)		
occurrences (all)	96		
Urinary tract infection			
subjects affected / exposed	49 / 486 (10.08%)		
occurrences (all)	67		
Influenza			
subjects affected / exposed	35 / 486 (7.20%)		
occurrences (all)	36		
Upper respiratory tract infection			
subjects affected / exposed	32 / 486 (6.58%)		
occurrences (all)	37		
Bronchitis			
subjects affected / exposed	29 / 486 (5.97%)		
occurrences (all)	36		
Conjunctivitis			
subjects affected / exposed	24 / 486 (4.94%)		
occurrences (all)	32		
Respiratory tract infection			
subjects affected / exposed	21 / 486 (4.32%)		
occurrences (all)	24		
Pharyngitis			
subjects affected / exposed	17 / 486 (3.50%)		
occurrences (all)	18		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	67 / 486 (13.79%)		
occurrences (all)	108		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2016	Protocol amendment 1: - List of Steering Committee members. - Revision of Background and Rationale Information to update clinical data related to fulvestrant and palbociclib, interaction of estrogens and cyclin-dependent kinases (CDK) in breast cancer. Addition of a new sub-section covering the rational for the translational sub-studies. - Addition of new inclusion criterion (inclusion criterion 2) to extend the study population to pre-menopausal women under treatment with luteinizing hormone releasing hormone (LHRH). - Clarification on inclusion criterion #6 that patient should have not received either hormonal treatment or chemotherapy in the metastatic setting. - Clarification on inclusion criterion #9 regarding the required value for ANC at baseline from 1.0 x 109/L to 1.5 x 109/L. - Replacement of the stratification criterion "prior vs. non-prior hormonal therapy" by "de novo vs. non de novo metastatic disease". - Implementation of translational sub-studies to evaluate the prognostic and predictive value of a variety of biomarkers involving blood and tumor sample collections at different time points. These molecular sub-studies will be implemented in selected centers. Participation of patients will be independent of their participation in the main clinical trial. - Recommendation for the use of erythropoietin-stimulating agents should be based on National Comprehensive Cancer Network (NCCN) guidelines. - Update on prohibited treatments and drug interactions. - Clarification on the requirements and time points for tumor assessment throughout the study. - Changes in the contact details (email and fax number) for expedite safety reporting. Removal of section 7.3 where it was described Sponsor responsibilities for safety updates to study funders and competent authorities.

30 June 2016	Protocol amendment 1b: - List of Steering Committee members - Revision of Background and Rationale Information to update clinical data related to fulvestrant and palbociclib, interaction of estrogens and CDK in breast cancer. Addition of a new sub-section covering the rational for the translational sub-studies - Modification of inclusion criterion 1 to extend the study population to pre-menopausal women under treatment with LHRH - Clarification on inclusion criterion 6 that patient should have not received either hormonal treatment or chemotherapy in the metastatic setting. - Clarification on inclusion criterion 9 regarding the required value for ANC at baseline from 1.0 x 109/L to 1.5 x 109/L. Clarification regarding acceptable values for alkaline phosphatase - Addition of new inclusion criterion (inclusion criterion 13) requiring patients consents to blood sample collection for biomarker research - Replacement of the stratification criterion “prior vs. non-prior hormonal therapy” by “de novo vs. non de novo metastatic disease” - Implementation of translational sub-studies to evaluate the prognostic and predictive value of a variety of biomarkers. Participation of patients in tumor tissue collection will be optional to their participation in the main clinical trial - Recommendation for the use of erythropoietin-stimulating agents should be based on NCCN guidelines - Update on prohibited treatments and drug interactions - Restriction of the requirement to perform baseline brain tumor assessment at time of screening only in patients with clinical suspicion of central involvement - Clarification on the requirements and time points for tumor assessment throughout the study - Harmonization of the protocol wording regarding timepoints and frequency to perform ECGs during the treatment period - Requirement for additional hemogram on C1D14 and C2D14 - Changes in the contact details for expedite safety report - Typographical, format and wording adjustments
30 June 2016	Protocol amendment 2: - Revision of Background and Rationale as per recent published data and update protocol with new data available on the IMPs used in the study. - Clarification on inclusion criterion #9 regarding acceptable values for alkaline phosphatase. - Addition of new inclusion criterion (inclusion criterion #13) as mandatory procedure the participation of patients in the translational sub-study for blood samples collection. - Typo correction on treatment schedule for palbociclib for Arm B, treatment period corrected from 28 days to 21 days of a 28-days cycle.

20 December 2016	Protocol amendment 3: - Revision of background information to include recent published data on palbociclib and fulvestrant on the treatment of ER+/HER2- metastatic breast cancer patients. - Revision of statistical assumptions leading to: • Modification of statistical assumptions regarding expected median PFS and Hazard Ratio for control vs. interventional arm. • Modification of primary variable from Progression free Survival at 1 year (1y-PFS) to overall PFS. • Change in sample size from 304 patients to 486 as result of updating the assumptions for its calculation. - Addition of new secondary end-points: Duration of Response and Time to Response. - Update on the definition of End of Study, EoS will occur one year after randomization of the last patient or when trial efficacy decision criteria are met, whichever is earlier. - Switch of analysis of primary end-point from superiority only to non-inferiority analyses, if the superiority criteria cannot be met. - Re-definition of interim analysis. Interim analysis was initially planned to occur after half of all expected patients have completed one-year follow-up period or have discontinued. Re-defined interim analysis will occur at 22 months after 35% of the total PFS events (89 events) have been observed. - Extend the justification of translational sub-studies analysis in the statistical section. - Addition of patient derived xenograft (PDX) models as potential studies to be performed from tumor samples obtained form patients enrolled in the study.
12 May 2017	Protocol amendment 4: - Revision of inclusion criteria #13 to request as mandatory procedure in the study the consent to provide tumor tissue samples. Patients must consent to provide tumor tissue samples at baseline and at time of progression (if biopsable lesion). For non de novo patients, tumor tissue at the time of metastatic disease diagnose will be requested as preferred option, though at least archived tissue samples from the primary tumor could be acceptable. - Revision of dose modifications guidelines for palbocilcib • Main changes affect the management of neutropenia during the first two cycles of treatment: Neutropenia grade 3 does not require immediate palbocilib treatment interruption but only if persists for more than 1 week. • In addition, dose modifications for QTc prolongations are aligned with the other non-hematologic toxicities based on later data showing that palbociclib does not prolong QTc interval. - Definition of maximum dose of corticosteroids as below of 10 mg per day of methylprednisolone equivalent.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported