Clinical trial results:
Neoadjuvant Letrozole and Palbociclib in patients with Stage II-IIIb breast cancer, HR (+) / HER2 (-) phenotype and Intermediate (18-25) or High (>25) Recurrence-Score by Oncotype-DX; analysis of RS and pathological changes at surgery.

Summary

EudraCT number	2018-001702-28
Trial protocol	ES
Global end of trial date	29 October 2020

Results information

Result version number	v1 (current)
This version publication date	28 May 2022
First version publication date	28 May 2022

Trial information

Trial identification

Sponsor protocol code	MedOPP199

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03819010
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medica Scientia Innovation Research (MEDSIR)
Sponsor organisation address	Avenida Diagonal 211, barcelona, Spain, 08018
Public contact	Alicia Garcia, Medica Scientia Innovation Research (MEDSIR), 34 932214135, alicia.garcia@medsir.org
Scientific contact	Alicia Garcia, Medica Scientia Innovation Research (MEDSIR), 932214135 932214135, 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	29 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 October 2020
Global end of trial reached?	Yes
Global end of trial date	29 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore after 6 months of treatment the ability of palbociclib in combination with letro-zole to induce global molecular changes measured by either the Oncotype DX Breast Recurrence Score® (the "Assay") test result at surgery (post-treatment Recurrence Score® (RS) result), or pathological Complete Response (pCR) in patients with aggres-sive luminal tumors (pre-treatment RS result 18-25 or 26-100, and Ki67>20).

Protection of trial subjects:

Standard of Care

Background therapy:

Palbociclib, initially known as PD-0332991, is an oral and selective inhibitor of cyclin-dependent kinase (CDK) 4/6. CDK4 and CDK6 promote cell-cycle entry by phosphorylating retinoblastoma (Rb) protein and other proteins in order to initiate cell transition from the G1 phase to the S phase in the cell cycle.

Evidence for comparator: -	
Actual start date of recruitment	05 May 2019
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: 67
Worldwide total number of subjects	67
EEA total number of subjects	67

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)	45

From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between May 2019 and Dec 2019, a total of 67 patients with HR+ and HER2- MBC were enrolled at 16 sites. Eligible patients entered one of the two available Cohorts (Cohort A RS 18-25; Cohort B RS 26-100) according to RS assessment: 33 patients in Cohort A and 34 patients in Cohort B

Pre-assignment

Screening details:

- Premenopausal and postmenopausal women ≥18 years of age.
- ECOG performance status ≤ 1.
- Histologically confirmed infiltrating breast cancer.
- Ki67 levels ≥ 20% confirmed by IHC testing.
- Tumor size > 2,0 cm (T2-4 according to TNM staging system).
- No metastatic disease (M0, according to TNM staging system).
- Adequate organ function.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A

Arm description:

Patients with pre-treatment RS 18-25

Arm type	Experimental
Investigational medicinal product name	Pablociclib + letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib: administered orally once a day for 21 days of every 28-day cycle followed by seven days off treatment.
Letrozole: administered orally once daily continuously (in all days of each cycle).
Patients should take palbociclib capsules with food. Patients should swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should take their dose at approximately the same time each day.

Arm title	Cohort B

Arm description:

patients with pre-treatment RS 26-100.

Arm type	Experimental
Investigational medicinal product name	Pablociclib + letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib: administered orally once a day for 21 days of every 28-day cycle followed by seven days off treatment.
Letrozole: administered orally once daily continuously (in all days of each cycle).

Patients should take palbociclib capsules with food. Patients should swallow palbociclib capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should take their dose at approximately the same time each day.

Number of subjects in period 1	Cohort A	Cohort B
Started	33	34
Completed	33	34

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A
Reporting group description: Patients with pre-treatment RS 18-25	
Reporting group title	Cohort B
Reporting group description: patients with pre-treatment RS 26-100.	

Reporting group values	Cohort A	Cohort B	Total
Number of subjects	33	34	67
Age categorical Units: Subjects			
Adults (18-64 years)	21	24	45
From 65-84 years	12	10	22
Gender categorical Units: Subjects			
Female	33	34	67
Male	0	0	0

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: all patients who received at least one dose of study medication and were evaluable for primary endpoints (biological stabilization or response)	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: All patients that accomplish selection criteria, receive at least one drug exposure, and receive the protocol required study drug exposure and processing. Criteria for determining the “per protocol” group assignment would be established by the Steering Committee before the statistical analysis begins.	
Subject analysis set title	Cohort A
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with pre-treatment RS 18-25	
Subject analysis set title	Cohort B
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with pre-treatment RS 26-100.	

Reporting group values	FAS	Per protocol	Cohort A
Number of subjects	67	65	33
Age categorical Units: Subjects			
Adults (18-64 years)	24	21	
From 65-84 years	10	10	

Gender categorical Units: Subjects			
Female	67	65	33
Male	0	0	0

Reporting group values	Cohort B		
Number of subjects	34		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years			
Gender categorical Units: Subjects			
Female	34		
Male	0		

End points

End points reporting groups

Reporting group title	Cohort A
Reporting group description: Patients with pre-treatment RS 18-25	
Reporting group title	Cohort B
Reporting group description: patients with pre-treatment RS 26-100.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description: all patients who received at least one dose of study medication and were evaluable for primary endpoints (biological stabilization or response)	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description: All patients that accomplish selection criteria, receive at least one drug exposure, and receive the protocol required study drug exposure and processing. Criteria for determining the "per protocol" group assignment would be established by the Steering Committee before the statistical analysis begins.	
Subject analysis set title	Cohort A
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with pre-treatment RS 18-25	
Subject analysis set title	Cohort B
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with pre-treatment RS 26-100.	

Primary: Primary Endpoint A

End point title	Primary Endpoint A
End point description: Percentage of patients in cohort A that experience a stable RS result as measured by the Assay after 6 months of treatment: from pre-treatment RS 18-25 to post-treatment RS≤25 or the percentage of patients with pre-treatment RS 18-25 or 26-100 that experience a biological response after 6 months of treatment defined by pCR (invasive) or microscopic residual infiltration where the post-treatment RS result is not feasible (reviewed by an independent pathologist).	
End point type	Primary
End point timeframe: After 6 months of treatment	

End point values	Cohort A	Cohort B	FAS	Cohort A
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	33	34	67	33
Units: Percentage of patients	33	34	67	33

Statistical analyses

Statistical analysis title	Co-Primary Efficacy Analysis

Statistical analysis description:

Percentage of patients in cohort A that experience a stable RS result as measured by the Assay after 6 months of treatment.

IMPORTANT: please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Comparison groups	Cohort A v Cohort A
Number of subjects included in analysis	66
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.7337
Method	exact binomial test

Primary: Primary Endpoint B

End point title	Primary Endpoint B

End point description:

The percentage of patients in cohort B that experience a change in RS result after 6 months of treatment: from pre-treatment RS 26-100 to post-treatment RS≤25; or The percentage of patients with pre-treatment RS 18-25 or 26-100 that experience a biological response after 6 months of treatment defined by pCR (invasive) or microscopic residual infiltration where the post-treatment RS result is not feasible (reviewed by anindependent pathologist).

End point type	Primary

End point timeframe:

After 6 months of treatment

End point values	Cohort A	Cohort B	FAS	Cohort B
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	33	34	67	34
Units: Percentage of pacients	33	34	67	34

Statistical analyses

Statistical analysis title	Co-primary B efficacy analysis

Statistical analysis description:

The percentage of patients in cohort B that experience a change in RS result after 6 months of treatment

IMPORTANT: please note that this is a single-arm study with no comparator arm. The number of subjects stated for the statistical analysis does not account for this design and is therefore stated as twice as high as the correct number of patients.

Comparison groups	Cohort B v Cohort B

Number of subjects included in analysis	68
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0001
Method	exact binomial test

Secondary: ORR

End point title	ORR

End point description:

ORR defined as the number of patients with complete response (CR) and partial response (PR) divided by the number of patients in the analysis population. Tumor response will be defined as best response, based on local investigator's assessment

End point type	Secondary

End point timeframe:

Before end of study

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: ORR	67			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of RS

End point title	Reduction of RS

End point description:

The percentage of patients that experience a change in RS result, as measured by median absolute value or median percentage after 6 months of treatment from pre-treatment RS 18-25 to post-treatment RS 0- 17 for patients in Cohort A and from pre-treatment RS 26-100 to post-treatment RS≤25 for patients in Cohort B.

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	Cohort A	Cohort B	FAS	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	34	67	
Units: Median absolute value or median % change	33	34	67	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in RCB score

End point title	Change in RCB score

End point description:

The percentage of patients that experience change in RCB score, which is calculated combining pathologic measurements of primary tumor (size and cellularity) and nodal metastases (number and size) from pre-treatment score of II-III to post-treatment score of 0-I for both Cohorts of patients.

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: RCB score	67			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Ki67

End point title	Change in Ki67

End point description:

The percentage of patients that experience a change in Ki67: from Ki67 ≥ 20 to <2.7 for both Cohorts of patients evaluated on surgical resected sample post-treatment (reviewed by an independent pathologist).

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Ki67	67			

Statistical analyses

No statistical analyses for this end point

Secondary: RS and RCB decrease in cohort B

End point title	RS and RCB decrease in cohort B

End point description:

Rate of patients in Cohort B for whom the RS result (from pre-treatment RS 26-100 to post-treatment RS≤25) and RCB score (from core II-III to 0-I) decrease; RCB score is calculated combining pathologic measurements of primary tumor and nodal metastasis.

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: RS and RCB score	33	34		

Statistical analyses

No statistical analyses for this end point

Secondary: RS change in cohort A

End point title	RS change in cohort A

End point description:

Rate of patients in Cohort A for whom the RS increases (from pre-treatment RS 18-25 to post-treatment RS 26-100).

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	Cohort A	Cohort B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: RS change	33	34		

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular changes

End point title	Molecular changes

End point description:

The concordance rate among post-treatment RS results, pCR (lack of signs of cancer), RCB, and PEPI scores; the latter is calculated combining assessment of tumor size, nodal involvement, HR status and Ki67 levels.

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Concordance rate	67			

Statistical analyses

No statistical analyses for this end point

Secondary: Determination of Ki67

End point title	Determination of Ki67

End point description:

Percentage of patients with Ki67>10% and Ki67<2.7 evaluated on tissue biopsy at 14 days.

End point type	Secondary

End point timeframe:

At 14 days

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: Ki67	67			

Statistical analyses

No statistical analyses for this end point

Secondary: change in RS

End point title	change in RS

End point description:

Median absolute value or median percentage of change in RS result from pre-treatment to post-treatment RS results in both Cohorts of patients after 6 months of treatment.

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: RS change	67			

Statistical analyses

No statistical analyses for this end point

Secondary: MTS

End point title	MTS

End point description:

MTS (maximum tumor shrinkage) defined as the percentage of tumor shrinkage from baseline, based on local investigator’s assessment

End point type	Secondary

End point timeframe:

After 6 months of treatment

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: MTS	67			

Statistical analyses

No statistical analyses for this end point

Secondary: breast conserving surgery

End point title	breast conserving surgery

End point description:

To determine the rate of breast conserving surgery.

End point type	Secondary

End point timeframe:

Before end of study

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: rate of breast conserving surgery	67			

Statistical analyses

No statistical analyses for this end point

Secondary: AEs

End point title	AEs

End point description:

Adverse events (AEs), which will be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Grade 3 and 4 AEs and serious adverse events (SAEs) will be assessed to determine the safety and tolerability of the drug combination.

End point type	Secondary

End point timeframe:

Before end of study

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	67			
Units: number of AEs	67			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting started on the first patient first dose (26th of February 2019)
The cut-off date for all safety analyses was 26th of October 2020.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5.0

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	3 / 67 (4.48%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infected seroma			
subjects affected / exposed	1 / 67 (1.49%)		
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	61 / 67 (91.04%)		
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	9 / 67 (13.43%)		
occurrences (all)	9		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	19 / 67 (28.36%)		
occurrences (all)	26		
Axillary pain			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	7 / 67 (10.45%)		
occurrences (all)	9		
influenza-like illness			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Mucosal dryness			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Oedema			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vulvovaginal dryness			

subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Anxiety			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Nervousness			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Investigations			
Alanina aminotransferasa increased			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	3		
Blood calcium increased			

subjects affected / exposed occurrences (all) Blood creatinine increased subjects affected / exposed occurrences (all) Glomerular filtration rate decreased subjects affected / exposed occurrences (all) Glomerular filtration rate increased subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1 5 / 67 (7.46%) 9 2 / 67 (2.99%) 4 1 / 67 (1.49%) 1		
Injury, poisoning and procedural complications Rib fracture subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Hypersomnia subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2 5 / 67 (7.46%) 5 1 / 67 (1.49%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) Thrombocytopenia	5 / 67 (7.46%) 6 10 / 67 (14.93%) 21 43 / 67 (64.18%) 118		

subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Retinal tear			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	5 / 67 (7.46%)		
occurrences (all)	6		
Dry Mouth			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Gastroesophageal reflux disease			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Odynophagia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Oesophagitis			

subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	2		
Rectal tenesmus			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	15 / 67 (22.39%)		
occurrences (all)	20		
Toothache			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Blister			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	3 / 67 (4.48%)		
occurrences (all)	3		
Rash vesicular			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Urticaria			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		

Renal and urinary disorders			
Nephropathy			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 67 (8.96%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Flank pain			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Muscle rigidity			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Musculoskeletal pain			
subjects affected / exposed	4 / 67 (5.97%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	1 / 67 (1.49%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 67 (2.99%)		
occurrences (all)	2		
Infections and infestations			

Conjunctivitis subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Cystitis subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Influenza subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Tooth abscess subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 67 (2.99%) 2		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		
Hypomagnesaemia subjects affected / exposed occurrences (all)	1 / 67 (1.49%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 March 2019	- Changes in efficacy secondary objectives. - Changes in inclusion criteria. - Changes in exclusion criteria. - Changes in study procedures. - Changes in statistic design. - Changes in treatment study. - Changes in study procedures.
19 August 2019	Changes in statistic design. There will be no interruption in recruitment while the interym analysis is performing.
12 December 2019	- We have specified in more detail the primary analyses. - New toxicity related to Palbociclibmamage :Intersticial lung Disease or Pneumonitis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported