



Clinical trial results:

The [PEARL] Study : Pet imaging as a biomarker of Everolimus Added value in hormone Refractory postmenopausal women

Summary

EudraCT number	2012-004860-22
Trial protocol	BE
Global end of trial date	06 July 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022
Summary attachment (see zip file)	PEARL_final_report (2012-004860-22-Final_study_report.pdf)

Trial information

Trial identification

Sponsor protocol code	IJB-BCTL:20120306
-----------------------	-------------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Institut Jules Bordet
Sponsor organisation address	Rue Meylemeersch,90, Brussels, Belgium, 1070
Public contact	Andrea Gombos, institut Jules Bordet, 32 2541 7232, andrea.gombos@bordet.be
Scientific contact	Andrea Gombos, institut Jules Bordet, 0472568124 2541 7232, andrea.gombos@bordet.be

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	09 August 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	06 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if early metabolic response (MR) using FDG-PET/CT is associated with progression free survival (PFS) in ER+, HER2 negative ABC or MBC patients treated with exemestane plus everolimus.

Protection of trial subjects:

insurance

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2014
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	Belgium: 64
Worldwide total number of subjects	64
EEA total number of subjects	64

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)	51
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Belgium

pilot phase - inclusion of patients from February 2014 till June 2016

main phase - inclusion of patients from June 2017 till May 2018

Pre-assignment

Screening details:

Screening assessments to confirm eligibility must be performed prior to the first dose of studydrug.

Physical examination including performance status, height and weight must be performed within 21 days prior to the first dose of study treatment.

Period 1

Period 1 title	Pilot and main phases
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Main phase

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5.0 mg and 10 mg strength for oral administration

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg strength for oral administration

Arm title	Pilot phase
------------------	-------------

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

5.0 mg and 10 mg strength for oral administration

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg strength for oral administration

Number of subjects in period 1	Main phase	Pilot phase
Started	20	44
Completed	20	27
Not completed	0	17
increase of liver function tests	-	1
not evaluable for PET	-	6
HER2+ on baseline biopsy	-	2
no PET measurable lesion	-	8

Period 2

Period 2 title	Evaluable subjects (ITT)
Is this the baseline period?	Yes ^[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Evaluable subjects (ITT)
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Everolimus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
5.0 mg and 10 mg strength for oral administration	
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

25 mg strength for oral administration

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics are provided for evaluable subjects.

Number of subjects in period 2^[2]	Evaluable subjects (ITT)
Started	47
Completed	47

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Analyzes have been performed on evaluable subjects.

Baseline characteristics

Reporting groups

Reporting group title	Evaluable subjects (ITT)
-----------------------	--------------------------

Reporting group description: -

Reporting group values	Evaluable subjects (ITT)	Total	
Number of subjects	47	47	
Age categorical			
Units: Subjects			

Age continuous			
Units: years			
arithmetic mean	57.1		
standard deviation	± 13.4	-	
Gender categorical			
Units: Subjects			
Female	47	47	
Male	0	0	
ECOG PS			
Units: Subjects			
Zero	23	23	
One	23	23	
Two	1	1	
Histology			
Units: Subjects			
Invasive ductal	38	38	
Invasive lobular	8	8	
Unknown	1	1	
Grade			
Units: Subjects			
G1	8	8	
G2	17	17	
G3	11	11	
Unknown	11	11	
Current disease status			
Units: Subjects			
Metastatic	45	45	
Locally advanced	2	2	
Current disease status			
Units: Subjects			
Metastatic Lung or liver	35	35	
Metastatic Bone only	6	6	
Metastatic Other	4	4	
Locally advanced	2	2	
N Metastatic sites			
Units: Subjects			
Zero	2	2	

12	24	24	
≥3	21	21	
KI67 (primary) Units: Subjects			
<10%	5	5	
10%15%	6	6	
16%25%	9	9	
>25%	17	17	
Unknown	10	10	
Prior CDK 4/6 Units: Subjects			
No	35	35	
Yes	12	12	
Number of lines CT in advanced setting Units: Subjects			
Zero	20	20	
One	14	14	
≥2	13	13	
Number of lines ET in advanced setting Units: Subjects			
Zero	2	2	
One	13	13	
≥2	32	32	
NSAI sensitive Units: Subjects			
No	13	13	
Yes	34	34	
Subjects who continued exemestane after having stopped everolimus Units: Subjects			
Yes	13	13	
No	34	34	
Subjects who continued exemestane more than a month after having stopped everolimus Units: Subjects			
Yes	5	5	
No	42	42	
Subjects with treatment interruption of exemestane (protocol violation) Units: Subjects			
Yes	1	1	
No	46	46	
Subjects with treatment interruption everolimus Units: Subjects			
Yes	23	23	
No	24	24	
Subjects with dose reduction everolimus (from 10 till 5) Units: Subjects			
Yes	21	21	
No	26	26	

Days between baseline PET and start treatment Units: Subjects			
1 - 7 days	36	36	
8-14 days	9	9	
≥15 days	2	2	
Days between start treatment and PET D14 Units: Subjects			
12	2	2	
13	5	5	
14	32	32	
15	6	6	
16	1	1	
17	1	1	
Duration everolimus treatment			
(=from start everolimus till last day everolimus)			
Units: months			
arithmetic mean	5.5		
standard deviation	± 5.2	-	
Duration everolimus treatment			
(=from start everolimus till last day everolimus)			
Units: months			
median	4.1		
full range (min-max)	1 to 29	-	
Duration exemestane treatment			
(= from start exemestane till last day exemestane)			
Units: months			
arithmetic mean	6.2		
standard deviation	± 5.5	-	
Duration exemestane treatment (in months)			
(= from start exemestane till last day exemestane)			
Units: months			
median	5		
full range (min-max)	1.6 to 29	-	

End points

End points reporting groups

Reporting group title	Main phase
Reporting group description: -	
Reporting group title	Pilot phase
Reporting group description: -	
Reporting group title	Evaluable subjects (ITT)
Reporting group description: -	
Subject analysis set title	F-FDG-PET/CT response on D14 Consist 25%
Subject analysis set type	Per protocol
Subject analysis set description: subjects with a SUVmax reduction of more than 25% in all lesions classified as responders	
Subject analysis set title	F-FDG-PET/CT non-response on D14 Consist 25%
Subject analysis set type	Per protocol
Subject analysis set description: subjects with a SUVmax reduction of less than or equal to 25% in all lesions classified as responders	
Subject analysis set title	F-FDG-PET/CT response on D14 Consist 15%("post-hoc")
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with a > 15 % homogenous decrease in maximum standardized uptake value (SUVmax) in all target lesions are considered as "responders". This is a "post-hoc" analysis, initially not scheduled by the study protocol.	
Subject analysis set title	F-FDG-PET/CT non-response on D14 Consist 15%("post-hoc")
Subject analysis set type	Sub-group analysis
Subject analysis set description: Subjects with a > 15 % homogenous decrease in maximum standardized uptake value (SUVmax) in all target lesions are considered as "responders". This is a "post-hoc" analysis, initially not scheduled by the study protocol.	

Primary: Time to progression

End point title	Time to progression
End point description:	
End point type	Primary
End point timeframe:	
Time to progression since date of early PET, in order to adjust for guarantee-time bias	

End point values	F-FDG-PET/CT response on D14 Consist 25%	F-FDG-PET/CT non-response on D14 Consist 25%	F-FDG-PET/CT response on D14 Consist 15%("post-hoc")	F-FDG-PET/CT non-response on D14 Consist 15%("post-hoc")
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	30	23	22
Units: months				
median (inter-quartile range (Q1-Q3))	6 (4.6 to 13.9)	3.1 (2.3 to 5.5)	6.4 (2.9 to 13.9)	2.2 (1.9 to 4.9)

Attachments (see zip file)	Kaplan–Meier plots/41523_2021_331_Fig1_HTML.jpeg Impact of variables on PFS (univariate analysis)
-----------------------------------	--

Statistical analyses

Statistical analysis title	PFS according to PET scan Consist 25% on D14
Statistical analysis description: subjects with > 25% homogenous decrease in maximum standardized uptake value (SUVmax) in all target lesions are considered as "responders"	
Comparison groups	F-FDG-PET/CT response on D14 Consist 25% v F-FDG-PET/CT non-response on D14 Consist 25%
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.44
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.5

Statistical analysis title	PFS according to PET scan Consist 15% on D14
Comparison groups	F-FDG-PET/CT response on D14 Consist 15%("post-hoc") v F-FDG-PET/CT non-response on D14 Consist 15%("post-hoc")
Number of subjects included in analysis	45
Analysis specification	Post-hoc
Analysis type	other
P-value	= 0.0032
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	0.72

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the first administration of study treatments until 28 days after the last dose of study treatments.

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

Dictionary used

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

Dictionary version	22.1
--------------------	------

Reporting groups

Reporting group title	Safety analysis
-----------------------	-----------------

Reporting group description:

Progression of underlying malignancy is not reported as an AE if it was clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE/AE. Clinical symptoms of progression may be reported as AEs or SAEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study. If there is any uncertainty about an AE being due to the disease under study, it should be reported as an AE or SAE. Clinical symptoms of underlying malignancy, even if they meet a seriousness criteria, should not be reported as SAE unless the investigator considers them as more severe than expected.

Serious adverse events	Safety analysis		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 55 (16.36%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial ischaemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Mucosal inflammation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchopneumopathy			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Interstitial lung disease			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Lung disorder			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			

subjects affected / exposed	2 / 55 (3.64%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Safety analysis		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 55 (90.91%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hot flush			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Hypertension			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Lymphoedema			

subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	8		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	11		
Chest pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	27 / 55 (49.09%)		
occurrences (all)	28		
General physical health deterioration			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hyperthermia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Inflammation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	28 / 55 (50.91%)		
occurrences (all)	36		
Oedema peripheral			

subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	7		
Pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Peripheral swelling			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Drug hypersensitivity			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Vulvovaginal dryness			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Vulvovaginal inflammation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Bronchospasm			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	13		
Dyspnoea			

subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	8		
Dysphonia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Dyspnoea exertional			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	21		
Epistaxis			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Interstitial lung disease			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Lung disorder			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Nasal dryness			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nasal ulcer			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pneumonitis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Psychiatric disorders			

Anxiety subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2		
Insomnia subjects affected / exposed occurrences (all)	5 / 55 (9.09%) 5		
Sleep disorder subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) Transaminases increased subjects affected / exposed occurrences (all) Weight decreased subjects affected / exposed occurrences (all) Weight increased subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 3 3 / 55 (5.45%) 3 5 / 55 (9.09%) 6 6 / 55 (10.91%) 6 1 / 55 (1.82%) 1		
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Limb injury subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1 1 / 55 (1.82%) 1		
Nervous system disorders Ageusia subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2		

Carpal tunnel syndrome subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Dizziness subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	3 / 55 (5.45%) 4		
Headache subjects affected / exposed occurrences (all)	10 / 55 (18.18%) 10		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Taste disorder subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	13 / 55 (23.64%) 14		
Hyperleukocytosis subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Neutropenia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 55 (7.27%) 4		
Ear and labyrinth disorders			

Vertigo subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Eye disorders Dry eye subjects affected / exposed occurrences (all) Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1 1 / 55 (1.82%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Anal fissure subjects affected / exposed occurrences (all) Anorectal discomfort subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dry mouth subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Dysphagia	1 / 55 (1.82%) 1 6 / 55 (10.91%) 6 2 / 55 (3.64%) 2 1 / 55 (1.82%) 1 7 / 55 (12.73%) 7 14 / 55 (25.45%) 15 1 / 55 (1.82%) 1 2 / 55 (3.64%) 2		

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Gastritis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Gastrointestinal disorder			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Haemorrhoids			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Nausea			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	8		
Oesophagitis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Proctalgia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	9		
Toothache			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Chest pain			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Alopecia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Dry skin			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	8		
Eczema			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nail toxicity			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Onychalgia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Onychoclasia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Photosensitivity reaction			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	8		
Rash			
subjects affected / exposed	17 / 55 (30.91%)		
occurrences (all)	21		
Rash maculo-papular			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Skin fissures			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Skin lesion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pollakiuria			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Renal pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hypothyroidism			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Bone pain			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	10		
Myalgia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Pain in jaw			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Infections and infestations			
Bartholin's abscess			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
Erysipelas			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Genital herpes simplex			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Localised infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Mastitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Pneumonia haemophilus			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Rhinitis			

subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Tracheitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Wound infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Skin injury			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 55 (34.55%)		
occurrences (all)	20		
Diabetes mellitus			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Dyslipidaemia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Hypercholesterolaemia			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	7		

Hypertriglyceridaemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Hypocalcaemia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hyponatraemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Vitamin B complex deficiency			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2014	Protocol v2.0 : -Clarification of haematology baseline assessments -Clarification of PET timelines -Change of efficacy assessment time point from every 8 weeks to 12 weeks to be in accordance with the reimbursement conditions for Afinitor in combination with exemestane.
15 May 2017	Protocol v3.0 - Add Pilot phase results (Second FDG PET/CT timepoint selected for the main phase) - Main phase sample size's recalculation - Modification of schedule of assessment - Modification of samples collection and translational researches - Clarification inclusion/exclusion criteria
20 June 2017	Protocol v4.0 : Modification of inclusion criteria
07 December 2020	Protocol v5.0 - Modification of the end of study definition - Modification of the secondary objective - Addition of a sample - Clarification regarding TR analyses

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 June 2016	Last subject included in the pilot phase of the study	22 May 2017

Notes:

Limitations and caveats

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

There were no limitations and caveats applicable to this summary of the results.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34548493>

<http://www.ncbi.nlm.nih.gov/pubmed/35296682>