Clinical trial results:
A Phase 1b/2 Randomized Study of MEDI-573 in Combination with an Aromatase Inhibitor (AI) Versus AI Alone in Women with Metastatic Breast Cancer (MBC)

Summary

EudraCT number	2011-000198-29
Trial protocol	ES DE HU BE GB
Global end of trial date	28 June 2019

Results information

Result version number	v1 (current)
This version publication date	14 June 2020
First version publication date	14 June 2020

Trial information

Trial identification

Sponsor protocol code	CD-ON-MEDI-573-1030

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01446159
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, 20878
Public contact	Mohammed Dar, One MedImmune Way, +1 301-398-1894, information.center@astrazeneca.com
Scientific contact	Mohammed Dar, MedImmune, LLC, +1 301-398-1894, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 August 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 June 2019
Global end of trial reached?	Yes
Global end of trial date	28 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the safety and tolerability of 3 dose levels of MEDI-573 in combination with an AI in participants with HR+, HER2-negative MBC.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 99
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Israel: 19
Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Belgium: 22
Worldwide total number of subjects	183
EEA total number of subjects	56

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)	96
From 65 to 84 years	84
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 10 countries (Belgium, Canada, France, Germany, Hungary, Israel, Spain, Poland, United Kingdom, USA).

Pre-assignment

Screening details:

A total of 187 participants were screened in the study. Of which, 183 participants were treated with study drugs.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	MEDI-573 10 mg/kg + aromatase inhibitor (AI)

Arm description:

Participants enrolled in Phase 1b of the study and received intravenous infusion of MEDI-573 10 mg/kg on Day 1 of each 21-day cycle and AI of the investigator’s choice (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Arm type	Experimental
Investigational medicinal product name	MEDI-573
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous (IV) infusion of MEDI-573 10 mg/kg on Day 1 of each 21-day cycle until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Investigational medicinal product name	Aromatase inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

AI of the investigator’s choice (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Arm title	MEDI-573 30 mg/kg + AI

Arm description:

Participants enrolled in Phase 1 b of the study and received intravenous infusion of MEDI-573 30 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Arm type	Experimental
Investigational medicinal product name	Aromatase inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

AI of the investigator’s choice (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Investigational medicinal product name	MEDI-573
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion of MEDI-573 10 mg/kg on Day 1 of each 21-day cycle until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Arm title	MEDI-573 45 mg/kg + AI

Arm description:

Participants received intravenous infusion of MEDI-573 45 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons. Three participants were enrolled in Phase 1b and 89 were enrolled in Phase 2 of the study.

Arm type	Experimental
Investigational medicinal product name	MEDI-573
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV infusion of MEDI-573 10 mg/kg on Day 1 of each 21-day cycle until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Investigational medicinal product name	Aromatase inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

AI of the investigator’s choice (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Arm title	Aromatase Inhibitor

Arm description:

Participants enrolled in Phase 2 of the study and received oral AI (letrozole, anastrozole, or exemestane) once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Arm type	Active comparator
Investigational medicinal product name	Aromatase Inhibitor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

aromatase inhibitor

Number of subjects in period 1	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI
Started	3	3	92
Completed	0	0	21
Not completed	3	3	71
Adverse event, serious fatal	2	3	43
Consent withdrawn by subject	1	-	14
Not specified	-	-	13
Lost to follow-up	-	-	1

Number of subjects in period 1	Aromatase Inhibitor
Started	85
Completed	23
Not completed	62
Adverse event, serious fatal	36
Consent withdrawn by subject	11
Not specified	13
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	MEDI-573 10 mg/kg + aromatase inhibitor (AI)
Reporting group description:	
Participants enrolled in Phase 1b of the study and received intravenous infusion of MEDI-573 10 mg/kg on Day 1 of each 21-day cycle and AI of the investigator's choice (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.	
Reporting group title	MEDI-573 30 mg/kg + AI
Reporting group description:	
Participants enrolled in Phase 1 b of the study and received intravenous infusion of MEDI-573 30 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.	
Reporting group title	MEDI-573 45 mg/kg + AI
Reporting group description:	
Participants received intravenous infusion of MEDI-573 45 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons. Three participants were enrolled in Phase 1b and 89 were enrolled in Phase 2 of the study.	
Reporting group title	Aromatase Inhibitor
Reporting group description:	
Participants enrolled in Phase 2 of the study and received oral AI (letrozole, anastrozole, or exemestane) once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.	

Reporting group values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI
Number of subjects	3	3	92
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2	1	49
From 65-84 years	1	2	41
85 years and over	0	0	2
Age Continuous Units: Years			
arithmetic mean	66.3	61.0	63.2
standard deviation	± 12.3	± 8.7	± 10.5
Sex: Female, Male Units: Participants			
Female	3	3	92
Male	0	0	0

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	6
White	2	3	84
More than one race	0	0	0
Unknown or Not Reported	0	0	2
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	7
Not Hispanic or Latino	3	3	85
Unknown or Not Reported	0	0	0

Reporting group values	Aromatase Inhibitor	Total	
Number of subjects	85	183	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	44	96	
From 65-84 years	40	84	
85 years and over	1	3	
Age Continuous Units: Years			
arithmetic mean	63.3		
standard deviation	± 11.0	-	
Sex: Female, Male Units: Participants			
Female	85	183	
Male	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	8	
White	82	171	
More than one race	0	0	
Unknown or Not Reported	1	3	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	6	13	
Not Hispanic or Latino	79	170	

Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	MEDI-573 10 mg/kg + aromatase inhibitor (AI)

Reporting group description:

Participants enrolled in Phase 1b of the study and received intravenous infusion of MEDI-573 10 mg/kg on Day 1 of each 21-day cycle and AI of the investigator's choice (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Reporting group title	MEDI-573 30 mg/kg + AI

Reporting group description:

Participants enrolled in Phase 1 b of the study and received intravenous infusion of MEDI-573 30 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Reporting group title	MEDI-573 45 mg/kg + AI

Reporting group description:

Participants received intravenous infusion of MEDI-573 45 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons. Three participants were enrolled in Phase 1b and 89 were enrolled in Phase 2 of the study.

Reporting group title	Aromatase Inhibitor

Reporting group description:

Participants enrolled in Phase 2 of the study and received oral AI (letrozole, anastrozole, or exemestane) once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Primary: Phase 1b and Phase 2: Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Phase 1b and Phase 2: Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)[1]

End point description:

An Adverse Event (AE) is any unfavourable and unintended sign, symptoms, or diseases temporally associated with use of study drug, whether or not considered related to study drug. A serious adverse event (SAE) is an AE that results in death, initial or prolonged inpatient hospitalization, life-threatening, persistent or significant disability/incapacity, congenital anomaly/birth defect, or an important medical event. TEAEs and TESAEs are defined as AEs and SAEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug, up to 60 days after the last study drug or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years). Safety population included all participants who received any study therapy and were analysed per the treatment they actually received was considered for this end point.

End point type	Primary

End point timeframe:

From the start of study treatment (Day 1) through 60 days after the last dose of treatment or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	92	85
Units: Participants				
Any TEAEs	3	3	90	82
Any TESAEs	2	0	21	16

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of Participants with dose-limiting toxicities (DLTs)

End point title	Phase 1b: Number of Participants with dose-limiting toxicities (DLTs)[2][3]

End point description:

The AEs that occurred during Cycle 1 (Days 1 to 21) and were suspected of having a causal relationship to MEDI-573 and were >= Grade 3 in severity were considered as DLTs. Evaluable population included all participants in Phase 1b of the study, who received at least 1 full cycle of MEDI-573 and completed the safety follow-up through the DLT evaluation period (Days 1 to 21 of Cycle 1) was considered for this end point.

End point type	Primary

End point timeframe:

Up to Day 21 of Cycle 1

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: Participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Phase 1b: Number of DLTs

End point title	Phase 1b: Number of DLTs[4][5]

End point description:

The AEs that occurred during Cycle 1 (Days 1 to 21) and were suspected of having a causal relationship to MEDI-573 and were >= Grade 3 in severity were considered as DLTs. Evaluable population included all participants in Phase 1b of the study, who received at least 1 full cycle of MEDI-573 and completed the safety follow-up through the DLT evaluation period (Days 1 to 21 of Cycle 1) was considered for this end point.

End point type	Primary

End point timeframe:

Up to Day 21 of Cycle 1

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.
[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	3	
Units: DLT events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Phase 2: Progression-free Survival (PFS)

End point title	Phase 2: Progression-free Survival (PFS)[6]

End point description:

Progression-free survival (PFS) was defined as the time from the randomization until the first documentation of disease progression or death due to any cause, whichever occurred first. The PFS was censored on the date of the last tumor assessment documenting absence of tumor progression for participants who had no documented progression and were still alive prior to data cut-off, dropout, or the initiation of alternate anticancer treatment. Progression is defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as >= 20% increase in the sum of diameters of target lesions and an absolute increase in sum of diameters of >=5mm (compared to the previous minimum sum) or progression of non-target lesions or a new lesion. The Intent-to-Treat (ITT) population included all participants who enrolled in Phase 2 and received any study therapy and were analysed per their randomized treatment group was considered for this end point.

End point type	Primary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first (Approximately 8 years)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Months				
median (confidence interval 95%)	12.65 (8.15 to 15.54)	11.33 (8.54 to 15.54)		

Statistical analyses

Statistical analysis title	Statistical analysis
Comparison groups	Aromatase Inhibitor v MEDI-573 45 mg/kg + AI
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.86
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.991
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.689
upper limit	1.429

Secondary: Phase 1b and Phase 2: Number of Participants With Abnormal Clinical Laboratory Results Reported as TEAEs

End point title	Phase 1b and Phase 2: Number of Participants With Abnormal Clinical Laboratory Results Reported as TEAEs

End point description:

An abnormal laboratory finding which required an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation were reported as AEs. The TEAEs are defined as AEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug, up to 60 days after the last study drug or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years). Safety population was considered for this end point.

End point type	Secondary

End point timeframe:

From the start of study treatment (Day 1) through 60 days after the last dose of treatment or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years)

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	92	85
Units: Participants				
Anemia	1	1	17	10
Eosinophilia	0	0	1	0
Leukopenia	0	0	0	3
Lymphopenia	0	0	1	2
Neutropenia	1	1	3	4
Pancytopenia	0	0	0	1
Thrombocytopenia	0	2	1	3
Granulocyte count decreased	0	1	0	0
Hemoglobin decreased	0	1	1	0
Lymphocyte count decreased	0	0	2	1
Monocyte count decreased	0	0	1	0
Neutrophil count decreased	0	0	2	0
Neutrophil count increased	0	0	1	0
Platelet count decreased	0	0	4	1
White blood cell count decreased	0	0	2	1
Alanine aminotransferase increased	2	0	8	4
Aspartate aminotransferase increased	2	1	6	4
Blood albumin decreased	0	0	1	0
Blood albumin increased	0	1	0	0
Blood alkaline phosphatase increased	0	1	5	5
Blood bicarbonate decreased	0	0	1	0
Blood bilirubin increased	0	0	0	1
Blood chloride decreased	0	0	1	0
Blood creatine increased	0	1	1	0
Blood creatinine decreased	0	0	0	1
Blood creatinine increased	0	1	8	2
Blood glucose increased	0	0	1	1
Blood lactate dehydrogenase increased	0	0	1	1
Blood magnesium decreased	0	1	0	0
Blood potassium decreased	0	0	1	0
Blood sodium decreased	0	1	0	0
Blood triglycerides increased	0	0	1	2
Blood urea increased	0	0	1	0
Blood uric acid increased	0	0	3	1
Gamma-glutamyl transferase decreased	0	1	0	0
Gamma-glutamyl transferase increased	1	1	9	4
Protein total decreased	0	1	0	1
Leukocytosis	0	0	0	1
Neutrophilia	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Number of Participants With Abnormal Vital Signs Reported as TEAEs

End point title	Phase 1b and Phase 2: Number of Participants With Abnormal Vital Signs Reported as TEAEs

End point description:

An abnormal vital signs that were judged by the investigator to be medically significant were reported as AEs. The TEAEs are defined as AEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug, up to 60 days after the last study drug or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years). Safety population was considered for this end point.

End point type	Secondary

End point timeframe:

From the start of study treatment (Day 1) through 60 days after the last dose of treatment or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years)

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	92	85
Units: Participants				
Bradycardia	1	0	1	1
Palpitations	1	0	1	2
Pyrexia	0	0	10	6
Temperature intolerance	0	0	1	1
Body temperature increased	0	0	1	0
Aspiration	0	0	1	0
Dyspnoea	2	0	18	14
Hypertension	0	0	8	13
Hypotension	1	0	1	0
Orthostatic hypotension	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Number of Participants with Abnormal Electrocardiogram (ECG) Reported as TEAEs

End point title	Phase 1b and Phase 2: Number of Participants with Abnormal Electrocardiogram (ECG) Reported as TEAEs

End point description:

An abnormal ECG findings that were judged by the investigator to be medically significant were reported as AEs. The TEAEs are defined as AEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug, up to 60 days after the last study drug or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years). Safety population was considered for this end point.

End point type	Secondary

End point timeframe:

From the start of study treatment (Day 1) through 60 days after the last dose of treatment or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years)

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	92	85
Units: Participants				
Sinus bradycardia	1	0	2	0
Sinus tachycardia	0	0	0	1
Supraventricular tachycardia	0	0	0	2
Tachycardia	0	0	1	2
Angina pectoris	0	0	0	1
Arrhythmia	0	0	0	1
Atrial fibrillation	0	0	1	2
Atrial flutter	0	0	0	1
Atrioventricular block first degree	0	0	1	0
Bradycardia	1	0	1	1
Cardiac failure	0	0	1	0
Cardiac valve disease	0	0	1	0
Palpitation	1	0	1	2
Ventricular extrasystoles	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Number of Participants With Best Overall Tumor Response

End point title	Phase 2: Number of Participants With Best Overall Tumor Response[7]

End point description:

Tumor evaluation was based on RECIST v1.1 by CT or MRI scan as: Complete Response (CR): Disappearance of all target and non-target lesions and no new lesions; Partial Response (PR): >= 30% decrease in the sum of diameters of target lesions (compared to baseline) and no new lesions; Stable disease (SD): Neither sufficient shrinkage to qualify as a response nor sufficient growth to qualify as progression; Progressive Disease (PD): >= 20% increase in the sum of diameters of target lesions and an absolute increase in sum of diameters of >=5mm (compared to the previous minimum sum) or progression of non-target lesions or a new lesion; not evaluable (NE): either no or only a subset of lesion measurements are made at an assessment. Participants enrolled in Phase 2 and were the part of IIT population were analysed.

End point type	Secondary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first (Approximately 8 years)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only those baseline period arms for which analysis was planned were reported in the end

point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Participants				
CR	1	2		
PR	23	21		
SD	48	46		
PD	15	12		
NE	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Objective Response Rate (ORR)

End point title	Phase 2: Objective Response Rate (ORR)[8]

End point description:

The ORR was defined as percentage of participants with confirmed complete response or confirmed partial response, where CR was defined as disappearance of all target and non-target lesions and no new lesions and PR was definded as >= 30% decrease in the sum of diameters of Target Lesions (compared to baseline) and no new lesions. Participants enrolled in Phase 2 and were the part of IIT population were analysed.

End point type	Secondary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first (Approximately 8 years)

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Percentage of participants				
number (confidence interval 95%)	27.0 (18.1 to 37.4)	27.1 (18.0 to 37.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Response

End point title	Phase 2: Time to Response[9]

End point description:

Time to response was measured from treatment start to the first documentation of disease response and was evaluated only in participants who achieved objective response (confirmed CR or confirmed PR. The CR was defined as disappearance of all target and non-target lesions and no new lesions and PR was defined as >= 30% decrease in the sum of diameters of Target Lesions (compared to baseline) and no new lesions. Participants enrolled in Phase 2 and were the part of IIT population were analysed.

End point type	Secondary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first (Approximately 8 years)

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Months				
median (full range (min-max))	4.22 (1.7 to 18.0)	3.98 (1.9 to 16.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Duration of Response (DR)

End point title	Phase 2: Duration of Response (DR)[10]

End point description:

Duration of response (DR) is measured from the first documentation of disease response to the first documented progressive disease and was evaluated only in participants who achieved objective response (confirmed CR or confirmed PR). The CR was defined as disappearance of all target and non-target lesions and no new lesions and PR was defined as >= 30% decrease in the sum of diameters of Target Lesions (compared to baseline) and no new lesions. Participants enrolled in Phase 2 and were the part of IIT population were analysed.

End point type	Secondary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first (Approximately 8 years)

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Months				
median (full range (min-max))	14.55 (4.5 to 58.8)	17.18 (2.1 to 45.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Time to Progression (TTP)

End point title	Phase 2: Time to Progression (TTP)[11]

End point description:

Time to progression was measured from treatment start until the first documentation of disease progression. The PD was defined as >= 20% increase in the sum of diameters of TLs and an absolute increase in sum of diameters of >=5mm (compared to the previous minimum sum) or progression of non-target lesions or a new lesion. Participants enrolled in Phase 2 and were the part of IIT population were analysed.

End point type	Secondary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first (Approximately 8 years)

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Months				
median (confidence interval 95%)	14.39 (8.34 to 18.69)	11.33 (8.54 to 17.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Overall Survival (OS)

End point title	Phase 2: Overall Survival (OS)[12]

End point description:

Overall survival (OS) was measured from treatment start until death. Participants enrolled in Phase 2 and were the part of IIT population were analysed.

End point type	Secondary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first

(Approximately 8 years)

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Months				
median (full range (min-max))	39.39 (0.3 to 73.2)	38.34 (0.3 to 51.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 2: Change in Tumor Size

End point title	Phase 2: Change in Tumor Size[13]

End point description:

Participants enrolled in Phase 2 and were the part of IIT population were analysed.

End point type	Secondary

End point timeframe:

From Day 1 until disease progression or death due to any cause, whichever occurred first (Approximately 8 years)

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	89	85		
Units: Centimeters				
arithmetic mean (standard deviation)	-36.2 (± 35.8)	-26.8 (± 37.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Area Under the Serum Concentration-time Curve From Time Zero to Day 21 (AUC0-day21) of MEDI-573 for Cycle 1

End point title	Phase 1b and Phase 2: Area Under the Serum Concentration-time Curve From Time Zero to Day 21 (AUC0-day21) of MEDI-573 for Cycle 1[14]

End point description:

The ITT population was considered for this analysis. Participants who received MEDI-573 were analysed.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 8, 15, and 21 (Cycle 2 Day 1, pre-dose)

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: µg·day/mL				
arithmetic mean (standard deviation)	1430 (± 867)	4500 (± 725)	7990 (± 1590)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Area Under the Serum Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of MEDI-573 for Cycle 1

End point title	Phase 1b and Phase 2: Area Under the Serum Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of MEDI-573 for Cycle 1[15]

End point description:

The ITT population was considered for this analysis. Participants who received MEDI-573 were analysed.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 8, 15, and 21 (Cycle 2 Day 1, pre-dose)

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: µg·day/mL				
arithmetic mean (standard deviation)	1500 (± 955)	4930 (± 691)	9570 (± 2310)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Dose-Normalised Area Under the Serum Concentration-time Curve From Time Zero to Infinity (DN AUC0-inf) of MEDI-573 for Cycle 1

End point title	Phase 1b and Phase 2: Dose-Normalised Area Under the Serum Concentration-time Curve From Time Zero to Infinity (DN AUC0-inf) of MEDI-573 for Cycle 1[16]

End point description:

The ITT population was considered for this analysis. Participants who received MEDI-573 were analysed.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 8, 15, and 21 (Cycle 2 Day 1, pre-dose)

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: day·kg·µg/mL/mg				
arithmetic mean (standard deviation)	150 (± 95.5)	164 (± 23.0)	213 (± 51.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Maximum Observed Serum Concentration (Cmax) of MEDI-573 for Cycle 1

End point title	Phase 1b and Phase 2: Maximum Observed Serum Concentration (Cmax) of MEDI-573 for Cycle 1[17]

End point description:

The ITT population was considered for this analysis. Participants who received MEDI-573 were analysed.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 8, 15, and 21 (Cycle 2 Day 1, pre-dose)

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: µg/mL				
arithmetic mean (standard deviation)	269 (± 74.1)	624 (± 210)	1070 (± 253)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Time to Reach Maximum Observed Serum Concentration (Tmax) of MEDI-573 for Cycle 1

End point title	Phase 1b and Phase 2: Time to Reach Maximum Observed Serum Concentration (Tmax) of MEDI-573 for Cycle 1[18]

End point description:

The ITT population was considered for this analysis. Participants who received MEDI-573 were analysed.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 8, 15, and 21 (Cycle 2 Day 1, pre-dose)

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: Day				
median (full range (min-max))	0.04 (0 to 0.09)	0.07 (0.06 to 0.08)	0.07 (0.03 to 0.17)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Systemic Clearance (CL) of MEDI-573 for Cycle 1

End point title	Phase 1b and Phase 2: Systemic Clearance (CL) of MEDI-573 for Cycle 1[19]

End point description:

The CL is a quantitative measure of the rate at which a drug substance is removed from the body. The total systemic clearance after intravenous dose was estimated by dividing the total administered dose by AUC(0-infinity). The ITT population was considered for this analysis. Participants who received MEDI-573 were analysed.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 8, 15, and 21 (Cycle 2 Day 1, pre-dose)

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: mL/day/kg				
arithmetic mean (standard deviation)	8.29 (± 3.86)	6.17 (± 0.889)	4.96 (± 1.13)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Terminal Half life (t1/2) of MEDI-573 for Cycle 1

End point title	Phase 1b and Phase 2: Terminal Half life (t1/2) of MEDI-573 for Cycle 1[20]

End point description:

The elimination half-life (t1/2) is the time measured for the serum concentration of MEDI-573 to decrease by 1 half to its original concentration. The ITT population was considered for this analysis. Participants who received MEDI-573 were analysed.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 8, 15, and 21 (Cycle 2 Day 1, pre-dose)

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: Day				
arithmetic mean (standard deviation)	4.38 (± 1.07)	5.91 (± 2.09)	8.45 (± 2.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Concentration of insulin-like growth factor (IGF) I and IGF-II

End point title	Phase 1b and Phase 2: Concentration of insulin-like growth factor (IGF) I and IGF-II

End point description:

The mean concentration profiles of both IGF-I and IGF-II post administration of MEDI-573 in plasma were evaluated during treatment. Safety population was analysed for this end point. Participants with free IGF concentration were analysed. The "n" denotes the number of participants who were analysed for the specific endpoint. The arbitrary numbers "9999" signifies that standard deviation was not calculated as only one participant was evaluable for the specified arm.

End point type	Secondary

End point timeframe:

Baseline (Cycle1 Day1 pre-dose), end of treatment (EOT), and 60 days post last dose (Approximately 8 years)

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	Aromatase Inhibitor
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	3	92	85
Units: ng/mL				
arithmetic mean (standard deviation)				
Baseline Free IGF-I (n=3, 3, 82, 78)	2.57 (± 0.712)	1.25 (± 0.635)	3.49 (± 4.39)	1.89 (± 1.24)
Baseline Free IGF-II (n=3, 3, 84, 78	3.81 (± 1.66)	3.07 (± 0.709)	3.01 (± 1.20)	3.03 (± 1.12)
EOT Free IGF-I (n=2, 2, 40, 38)	0.724 (± 0.421)	0.313 (± 0.0)	0.346 (± 0.130)	2.32 (± 3.64)
EOT Free IGF-II (n=2, 2, 40, 38)	0.625 (± 0.0)	0.625 (± 0.0)	0.641 (± 0.102)	3.12 (± 1.22)
60 days post last dose Free IGF-I (n=1, 2, 21, 22)	1.54 (± 99999)	1.33 (± 0.3)	1.02 (± 1.29)	4.62 (± 8.52)
60days post last dose Free IGF-II (n=1, 2, 21, 22)	1.49 (± 99999)	0.625 (± 0.0)	0.984 (± 0.734)	3.38 (± 1.51)

Statistical analyses

No statistical analyses for this end point

Secondary: Phase 1b and Phase 2: Number of participants With Positive Anti-drug Antibodies (ADA) to MEDI-573

End point title	Phase 1b and Phase 2: Number of participants With Positive Anti-drug Antibodies (ADA) to MEDI-573[21]

End point description:

Participants With Positive ADA to MEDI-573 are reported. Participants who received MEDI-573 and were analysed per the treatment they actually received were analysed for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion on Day 1 of each cycle, End of Treatment, Day 30, 60 and 90 post treatment (approximately 8 years)

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only those baseline period arms for which analysis was planned were reported in the end point.

End point values	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3	3	92	
Units: Participants	0	0	1	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug (Day 1) through 60 days after the last dose of treatment or until the participants started another anticancer therapy, whichever occurs first (approximately 8 years)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	MEDI-573 10 mg/kg + aromatase inhibitor (AI)

Reporting group description:

Participants enrolled in Phase 1b of the study and received intravenous infusion of MEDI-573 10 mg/kg on Day 1 of each 21-day cycle and AI of the investigator's choice (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Reporting group title	MEDI-573 30 mg/kg + AI

Reporting group description:

Participants enrolled in Phase 1 b of the study and received intravenous infusion of MEDI-573 30 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Reporting group title	MEDI-573 45 mg/kg + AI

Reporting group description:

Participants received intravenous infusion of MEDI-573 45 mg/kg on Day 1 of each 21-day cycle and AI (letrozole, anastrozole, or exemestane) orally once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons. Three participants were enrolled in Phase 1b and 89 were enrolled in Phase 2 of the study.

Reporting group title	Aromatase Inhibitor

Reporting group description:

Participants enrolled in Phase 2 of the study and received oral AI (letrozole, anastrozole, or exemestane) once daily until unacceptable toxicity, documentation of disease progression, or withdrawal for other reasons.

Serious adverse events	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	21 / 92 (22.83%)
number of deaths (all causes)	2	3	43
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER METASTATIC			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
INTRADUCTAL PROLIFERATIVE BREAST LESION			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUNG ADENOCARCINOMA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OVARIAN CANCER METASTATIC			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RECTAL NEOPLASM			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UTERINE CANCER			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
EMBOLISM			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOTENSION			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

PYREXIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
ASPIRATION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EMPHYSEMA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMOTHORAX			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
MENTAL STATUS CHANGES			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
ACETABULUM FRACTURE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CERVICAL VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HAEMATOMA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FLUTTER			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

CARDIAC FAILURE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SINUS BRADYCARDIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARTIAL SEIZURES			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPHAGIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC ULCER PERFORATION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INTESTINAL MASS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PANCREATITIS ACUTE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SMALL INTESTINAL OBSTRUCTION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 92 (3.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
BILIARY DILATATION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal and urinary disorders			
HYDRONEPHROSIS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
BACK PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FLANK PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
CELLULITIS			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULITIS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Aromatase Inhibitor		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 85 (18.82%)		
number of deaths (all causes)	36		
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BREAST CANCER METASTATIC			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
INTRADUCTAL PROLIFERATIVE BREAST LESION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LUNG ADENOCARCINOMA			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
OVARIAN CANCER METASTATIC			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
RECTAL NEOPLASM			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
UTERINE CANCER			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
EMBOLISM			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPOTENSION			

subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
CHEST PAIN			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PYREXIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
OVARIAN CYST			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
ASPIRATION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
EMPHYSEMA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
PLEURAL EFFUSION			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
PNEUMOTHORAX			

subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
PULMONARY EMBOLISM				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
MENTAL STATUS CHANGES				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
PSYCHOTIC DISORDER				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SUICIDE ATTEMPT				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
ACETABULUM FRACTURE				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
CERVICAL VERTEBRAL FRACTURE				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
SUBDURAL HAEMATOMA				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders			
ATRIAL FIBRILLATION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ATRIAL FLUTTER			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CARDIAC FAILURE			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SINUS BRADYCARDIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
SUPRAVENTRICULAR TACHYCARDIA			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
ALTERED STATE OF CONSCIOUSNESS			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CEREBRAL HAEMORRHAGE			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

PARTIAL SEIZURES				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
FEBRILE NEUTROPENIA				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
ABDOMINAL PAIN				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ABDOMINAL PAIN UPPER				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DIARRHOEA				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
DYSPHAGIA				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
GASTRIC ULCER PERFORATION				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
INTESTINAL MASS				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

PANCREATITIS ACUTE				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
SMALL INTESTINAL OBSTRUCTION				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
VOMITING				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
BILIARY DILATATION				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
HYDRONEPHROSIS				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
BACK PAIN				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
FLANK PAIN				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
MUSCULOSKELETAL CHEST PAIN				

subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
CELLULITIS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DEVICE RELATED INFECTION			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
DIVERTICULITIS			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
WOUND INFECTION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
DEHYDRATION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
HYPONATRAEMIA			

subjects affected / exposed	0 / 85 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	MEDI-573 10 mg/kg + aromatase inhibitor (AI)	MEDI-573 30 mg/kg + AI	MEDI-573 45 mg/kg + AI
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	90 / 92 (97.83%)
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	13 / 92 (14.13%)
occurrences (all)	1	1	22
HYPERTENSION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	8 / 92 (8.70%)
occurrences (all)	0	0	17
PERIPHERAL COLDNESS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	19 / 92 (20.65%)
occurrences (all)	1	0	33
FATIGUE			
subjects affected / exposed	2 / 3 (66.67%)	3 / 3 (100.00%)	41 / 92 (44.57%)
occurrences (all)	3	6	96
MUCOSAL INFLAMMATION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	7 / 92 (7.61%)
occurrences (all)	0	0	9
OEDEMA PERIPHERAL			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	9 / 92 (9.78%)
occurrences (all)	0	0	16
PAIN			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	1	0	2
PYREXIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	9 / 92 (9.78%)
occurrences (all)	0	0	11
SWELLING			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
ATROPHIC VULVOVAGINITIS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences (all)	1	0	1
BREAST HAEMORRHAGE			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
BREAST PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	4 / 92 (4.35%)
occurrences (all)	0	0	5
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	19 / 92 (20.65%)
occurrences (all)	0	1	27
DYSPNOEA			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	18 / 92 (19.57%)
occurrences (all)	2	0	21
DYSPNOEA EXERTIONAL			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 92 (3.26%)
occurrences (all)	1	0	7
EPISTAXIS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	0	0	5
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 92 (6.52%)
occurrences (all)	0	0	7
Psychiatric disorders			

ANXIETY			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	10 / 92 (10.87%)
occurrences (all)	0	1	13
CONFUSIONAL STATE			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 92 (1.09%)
occurrences (all)	0	1	1
DEPRESSION			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	11 / 92 (11.96%)
occurrences (all)	1	1	12
ENURESIS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
INSOMNIA			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	10 / 92 (10.87%)
occurrences (all)	0	1	12
TACHYPHRENIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	8 / 92 (8.70%)
occurrences (all)	2	0	13
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	6 / 92 (6.52%)
occurrences (all)	7	1	14
BLOOD ALBUMIN INCREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	5 / 92 (5.43%)
occurrences (all)	0	1	11
BLOOD CHOLESTEROL INCREASED			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	1	0	3
BLOOD CREATINE INCREASED			

subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 92 (1.09%)
occurrences (all)	0	1	1
BLOOD CREATININE INCREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	8 / 92 (8.70%)
occurrences (all)	0	1	38
BLOOD MAGNESIUM DECREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
BLOOD SODIUM DECREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
GAMMA-GLUTAMYLTRANSFERASE DECREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	9 / 92 (9.78%)
occurrences (all)	1	3	41
GRANULOCYTE COUNT DECREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	2	0
HAEMOGLOBIN DECREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 92 (1.09%)
occurrences (all)	0	1	4
PROTEIN TOTAL DECREASED			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
WEIGHT DECREASED			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	6 / 92 (6.52%)
occurrences (all)	0	2	10
WEIGHT INCREASED			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	0	0	5
Injury, poisoning and procedural complications			

FALL			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	3 / 92 (3.26%)
occurrences (all)	0	0	4
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences (all)	1	0	1
PALPITATIONS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences (all)	1	0	1
SINUS BRADYCARDIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	1	0	2
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	16 / 92 (17.39%)
occurrences (all)	2	0	25
DYSGEUSIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	13 / 92 (14.13%)
occurrences (all)	1	0	16
HEADACHE			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	20 / 92 (21.74%)
occurrences (all)	0	1	29
NEUROPATHY PERIPHERAL			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	3	0	2
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	17 / 92 (18.48%)
occurrences (all)	2	3	48
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
LYMPHADENOPATHY			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences (all)	1	0	1
NEUTROPENIA			

subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 92 (3.26%)
occurrences (all)	6	1	6
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	1 / 92 (1.09%)
occurrences (all)	0	3	2
Eye disorders			
DRY EYE			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	0	0	6
PHOTOPSIA			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
VISION BLURRED			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	1	0	9
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	7 / 92 (7.61%)
occurrences (all)	0	0	8
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	0	0	6
CONSTIPATION			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	21 / 92 (22.83%)
occurrences (all)	4	1	27
DIARRHOEA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	30 / 92 (32.61%)
occurrences (all)	3	0	50
DRY MOUTH			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	1	0	7
DYSPEPSIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 92 (6.52%)
occurrences (all)	0	0	6
HAEMATOCHEZIA			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
NAUSEA			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	34 / 92 (36.96%)
occurrences (all)	1	3	53
PROCTALGIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
STOMATITIS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 92 (6.52%)
occurrences (all)	0	0	11
VOMITING			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	14 / 92 (15.22%)
occurrences (all)	0	0	20
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	8 / 92 (8.70%)
occurrences (all)	0	0	10
ECCHYMOSIS			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences (all)	2	0	3
NIGHT SWEATS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 92 (3.26%)
occurrences (all)	1	0	3
PRURITUS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	13 / 92 (14.13%)
occurrences (all)	1	0	15
RASH			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	11 / 92 (11.96%)
occurrences (all)	0	0	12
SKIN MASS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
BLADDER SPASM			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
DYSURIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 92 (1.09%)
occurrences (all)	1	0	1
POLLAKIURIA			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	0	0	2
URINARY HESITATION			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 92 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	28 / 92 (30.43%)
occurrences (all)	2	1	60
BACK PAIN			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	29 / 92 (31.52%)
occurrences (all)	0	1	49
BONE LOSS			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
BONE PAIN			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	9 / 92 (9.78%)
occurrences (all)	3	0	9
FLANK PAIN			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	1	0	2
GROIN PAIN			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 92 (2.17%)
occurrences (all)	0	1	2
MUSCLE SPASMS			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	10 / 92 (10.87%)
occurrences (all)	0	2	12
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	12 / 92 (13.04%)
occurrences (all)	4	1	15
MUSCULOSKELETAL PAIN			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	10 / 92 (10.87%)
occurrences (all)	2	0	13
MYALGIA			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	9 / 92 (9.78%)
occurrences (all)	5	1	10
NECK PAIN			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 92 (6.52%)
occurrences (all)	0	0	7
PAIN IN EXTREMITY			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	14 / 92 (15.22%)
occurrences (all)	0	0	20
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	0	0	2
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
FUNGAL SKIN INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	1	0
INFLUENZA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	1	0	2
LIP INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 92 (0.00%)
occurrences (all)	0	3	0
NAIL INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 92 (1.09%)
occurrences (all)	0	1	1
SINUSITIS			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	4 / 92 (4.35%)
occurrences (all)	0	1	4

UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	9 / 92 (9.78%)
occurrences (all)	0	0	11
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	26 / 92 (28.26%)
occurrences (all)	1	1	48
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	6 / 92 (6.52%)
occurrences (all)	0	0	7
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	19 / 92 (20.65%)
occurrences (all)	1	0	24
DEHYDRATION			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 92 (1.09%)
occurrences (all)	0	1	2
DIABETES MELLITUS			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 92 (3.26%)
occurrences (all)	1	0	5
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	10 / 92 (10.87%)
occurrences (all)	0	5	38
HYPERKALAEMIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	1	0	5
HYPERMAGNESAEMIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	1	0	2
HYPERURICAEMIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	5 / 92 (5.43%)
occurrences (all)	1	0	6
HYPOCALCAEMIA			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	7 / 92 (7.61%)
occurrences (all)	3	0	15
HYPOKALAEMIA			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	10 / 92 (10.87%)
occurrences (all)	0	0	18
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	6 / 92 (6.52%)
occurrences (all)	1	1	9
HYPONATRAEMIA			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	3 / 92 (3.26%)
occurrences (all)	5	0	16
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 92 (2.17%)
occurrences (all)	3	0	2

Non-serious adverse events	Aromatase Inhibitor		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 85 (96.47%)		
Vascular disorders			
HOT FLUSH			
subjects affected / exposed	30 / 85 (35.29%)		
occurrences (all)	46		
HYPERTENSION			
subjects affected / exposed	13 / 85 (15.29%)		
occurrences (all)	24		
PERIPHERAL COLDNESS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	13 / 85 (15.29%)		
occurrences (all)	18		
FATIGUE			
subjects affected / exposed	27 / 85 (31.76%)		
occurrences (all)	38		
MUCOSAL INFLAMMATION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
OEDEMA PERIPHERAL			

subjects affected / exposed	10 / 85 (11.76%)		
occurrences (all)	20		
PAIN			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
PYREXIA			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	11		
SWELLING			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
Reproductive system and breast disorders			
ATROPHIC VULVOVAGINITIS			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
BREAST HAEMORRHAGE			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
BREAST PAIN			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	9		
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	11 / 85 (12.94%)		
occurrences (all)	16		
DYSPNOEA			
subjects affected / exposed	14 / 85 (16.47%)		
occurrences (all)	23		
DYSPNOEA EXERTIONAL			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	2		
EPISTAXIS			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	5		
OROPHARYNGEAL PAIN			

subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	4		
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	10		
CONFUSIONAL STATE			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
DEPRESSION			
subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	4		
ENURESIS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
INSOMNIA			
subjects affected / exposed	13 / 85 (15.29%)		
occurrences (all)	14		
TACHYPHRENIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	5		
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	7		
BLOOD ALBUMIN INCREASED			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	5 / 85 (5.88%)		
occurrences (all)	10		
BLOOD CHOLESTEROL INCREASED			

subjects affected / exposed	2 / 85 (2.35%)			
occurrences (all)	3			
BLOOD CREATINE INCREASED				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences (all)	0			
BLOOD CREATININE INCREASED				
subjects affected / exposed	2 / 85 (2.35%)			
occurrences (all)	2			
BLOOD MAGNESIUM DECREASED				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences (all)	0			
BLOOD SODIUM DECREASED				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences (all)	0			
GAMMA-GLUTAMYLTRANSFERASE DECREASED				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences (all)	0			
GAMMA-GLUTAMYLTRANSFERASE INCREASED				
subjects affected / exposed	4 / 85 (4.71%)			
occurrences (all)	5			
GRANULOCYTE COUNT DECREASED				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences (all)	0			
HAEMOGLOBIN DECREASED				
subjects affected / exposed	0 / 85 (0.00%)			
occurrences (all)	0			
PROTEIN TOTAL DECREASED				
subjects affected / exposed	1 / 85 (1.18%)			
occurrences (all)	2			
WEIGHT DECREASED				
subjects affected / exposed	5 / 85 (5.88%)			
occurrences (all)	7			
WEIGHT INCREASED				

subjects affected / exposed	3 / 85 (3.53%)		
occurrences (all)	3		
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	6		
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
PALPITATIONS			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	3		
SINUS BRADYCARDIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
DIZZINESS			
subjects affected / exposed	9 / 85 (10.59%)		
occurrences (all)	12		
DYSGEUSIA			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	8		
HEADACHE			
subjects affected / exposed	19 / 85 (22.35%)		
occurrences (all)	27		
NEUROPATHY PERIPHERAL			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	10 / 85 (11.76%)		
occurrences (all)	18		
INCREASED TENDENCY TO BRUISE			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		

LYMPHADENOPATHY			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
NEUTROPENIA			
subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	8		
THROMBOCYTOPENIA			
subjects affected / exposed	3 / 85 (3.53%)		
occurrences (all)	11		
Eye disorders			
DRY EYE			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	7		
PHOTOPSIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
VISION BLURRED			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	2		
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	9		
ABDOMINAL PAIN UPPER			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	9		
CONSTIPATION			
subjects affected / exposed	23 / 85 (27.06%)		
occurrences (all)	32		
DIARRHOEA			
subjects affected / exposed	22 / 85 (25.88%)		
occurrences (all)	39		
DRY MOUTH			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	13		
DYSPEPSIA			

subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	8		
HAEMATOCHEZIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
NAUSEA			
subjects affected / exposed	30 / 85 (35.29%)		
occurrences (all)	46		
PROCTALGIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
STOMATITIS			
subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	9		
VOMITING			
subjects affected / exposed	15 / 85 (17.65%)		
occurrences (all)	21		
Skin and subcutaneous tissue disorders			
ALOPECIA			
subjects affected / exposed	11 / 85 (12.94%)		
occurrences (all)	12		
ECCHYMOSIS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
NIGHT SWEATS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
PRURITUS			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	9		
RASH			
subjects affected / exposed	10 / 85 (11.76%)		
occurrences (all)	15		
SKIN MASS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		

Renal and urinary disorders			
BLADDER SPASM			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
DYSURIA			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
POLLAKIURIA			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	7		
URINARY HESITATION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	35 / 85 (41.18%)		
occurrences (all)	73		
BACK PAIN			
subjects affected / exposed	21 / 85 (24.71%)		
occurrences (all)	33		
BONE LOSS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
BONE PAIN			
subjects affected / exposed	9 / 85 (10.59%)		
occurrences (all)	11		
FLANK PAIN			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
GROIN PAIN			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
MUSCLE SPASMS			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	14		
MUSCULOSKELETAL CHEST PAIN			

subjects affected / exposed	11 / 85 (12.94%)		
occurrences (all)	14		
MUSCULOSKELETAL PAIN			
subjects affected / exposed	11 / 85 (12.94%)		
occurrences (all)	12		
MYALGIA			
subjects affected / exposed	10 / 85 (11.76%)		
occurrences (all)	11		
NECK PAIN			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	8		
PAIN IN EXTREMITY			
subjects affected / exposed	18 / 85 (21.18%)		
occurrences (all)	43		
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	6 / 85 (7.06%)		
occurrences (all)	7		
DEVICE RELATED INFECTION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
FUNGAL SKIN INFECTION			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	3		
INFLUENZA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
LIP INFECTION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
NAIL INFECTION			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
SINUSITIS			
subjects affected / exposed	3 / 85 (3.53%)		
occurrences (all)	4		

UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	10 / 85 (11.76%)		
occurrences (all)	13		
URINARY TRACT INFECTION			
subjects affected / exposed	17 / 85 (20.00%)		
occurrences (all)	26		
VIRAL UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	7 / 85 (8.24%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	14 / 85 (16.47%)		
occurrences (all)	16		
DEHYDRATION			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	2		
DIABETES MELLITUS			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		
HYPERGLYCAEMIA			
subjects affected / exposed	8 / 85 (9.41%)		
occurrences (all)	12		
HYPERKALAEMIA			
subjects affected / exposed	3 / 85 (3.53%)		
occurrences (all)	13		
HYPERMAGNESAEMIA			
subjects affected / exposed	3 / 85 (3.53%)		
occurrences (all)	6		
HYPERURICAEMIA			
subjects affected / exposed	2 / 85 (2.35%)		
occurrences (all)	3		
HYPOCALCAEMIA			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	1		
HYPOKALAEMIA			

subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	12		
HYPOMAGNESAEMIA			
subjects affected / exposed	1 / 85 (1.18%)		
occurrences (all)	2		
HYPONATRAEMIA			
subjects affected / exposed	4 / 85 (4.71%)		
occurrences (all)	7		
HYPOPHOSPHATAEMIA			
subjects affected / exposed	0 / 85 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2012	Sections of clinical experience with medi-573, research hypothesis, research hypothesis were updated. Primary objective was updated for the number of dose levels to be tested from 2 to 3. The text of Phase 1b (Dose-evaluation Phase) was modified to account for the addition of a 45 mg/kg plus AI treatment arm. Phase 2 (Randomization Phase) was changed to a 2-arm structure to test 45 mg/kg MEDI-573 plus AI versus AI alone. Addition of a 45 mg/kg arm in Phase 1b and Phase 2, based on PK and pharmacodynamic experience. Inclusion criteria added for participants with metastases to bone, clarified that HER2 negativity assessment, added the definition of postmenopausal, and added the age limit for participants enrolled in Japan. Exclusion criteria changed for the washout period following tamoxifen or an AI prior to receiving the first dose of MEDI-573, clarified the exclusion of participants with active brain metastases, known central nervous system metastases, and leptomeningeal carcinomatosis; text was modified for participants with a history of allergy or reaction attributed to compounds of chemical/biologic composition similar to MEDI-573 or AI, for history of another invasive malignancy, and had poorly controlled diabetes mellitus. Modified the randomization text. Added the text related to dairy for AI intake. Clarified the for MEDI-573 infusion timing. Updated the "Schedule of Study Procedures" table. Added additional physical examination details. Planned analyses text was changed to specify that the primary analysis of PFS and safety were performed after 122 PFS events had occurred. Modified sample size and power calculations.
05 December 2012	Randomization statement was added for participants with bone-only disease. Inclusion criteria were updated for participants with bone metastases and method of determining HER2 status. Exclusion criteria were updated for prior adjuvant therapy with an AI and/or tamoxifen and participants with evidence of spinal canal involvement. Added treatment window period to infusion times for potential overfill and for collection of vital signs. Updated permitted concomitant medications section. Updated the "Schedule of Study Procedures" table. Screening section was modified for laboratory results, pregnancy tests, and archival tumor samples. Modified the statements related to Cycle 1 Day 1 and Cycle 2 and Every Cycle Thereafter assessments. Added the description of assessments required after 2 years on study for participants who remain on study drug or s who were discontinued study drug.
25 July 2016	Updated the text to include the results from the completed FTIH study (CP-184) and the primary analysis of CD-ON-MEDI-573-1030 study. Updated "End of study" to clarify the follow-up procedures for participants who discontinued treatment or for participants who were on treatment at the end of 36 months. Updated the "Schedule of Study Procedures" table.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported