



Clinical trial results:

A Randomized Phase II Study of Fulvestrant in Combination with the dual mTOR Inhibitor AZD2014 or Everolimus or Fulvestrant alone in Estrogen Receptor Positive Advanced or Metastatic Breast Cancer.

Summary

EudraCT number	2013-002403-34
Trial protocol	DE PT ES HU FR
Global end of trial date	31 December 2021

Results information

Result version number	v1 (current)
This version publication date	25 March 2023
First version publication date	25 March 2023
Summary attachment (see zip file)	JAMA Oncology Publication (jamaoncology_schmid_2019_oi_190056.pdf) Adverse Event Summary (EudraCT Adverse events summary 16Dec2022.pdf)

Trial information

Trial identification

Sponsor protocol code	009175QM
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02216786
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Mile End Road, London, United Kingdom, E1 2EF
Public contact	Centre for Experimental Cancer Medicine, Queen Mary University of London, +44 02078828490, bci-MANTA@qmul.ac.uk
Scientific contact	Centre for Experimental Cancer Medicine, Queen Mary University of London, +44 02078828490, bci-MANTA@qmul.ac.uk

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	31 March 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 October 2017
Global end of trial reached?	Yes
Global end of trial date	31 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main aims of this study are to:

- Determine whether dual inhibition of mTORC 1 and mTORC2 with AZD2014 will increase the antitumour activity of endocrine treatment with fulvestrant in ER positive advanced or metastatic breast cancer.
- Determine whether inhibition of both mTORC 1 and mTORC2 using AZD2014 will have superior antitumour activity compared to inhibition of mTORC1 alone with everolimus, when combined with fulvestrant.
- Explore whether additional efficacy is likely to be present in a subgroup with PI3K pathway activation for whom it is hypothesised that there will be greater sensitivity to mTOR inhibitors
- Characterize the patient population who might benefit from fulvestrant plus AZD2014 to identify potential predictors of sensitivity

The primary objectives of this study are to:

- Estimate the clinical benefit (CB) of fulvestrant+AZD2014 relative to fulvestrant+everolimus or fulvestrant alone, as measured by investigator assessed progression free survival (PFS)

Protection of trial subjects:

Eligibility criteria for this study were selected to enhance the safety of patients in this trial. A number of exclusion criteria were specifically based on the known safety profiles of the study drug treatments, including the known safety profile of everolimus, as well as nonclinical and clinical data for AZD2014.

All enrolled patients were evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study. Safety evaluations consisted of medical interviews, recording of adverse events, physical examinations, and laboratory measurements. Patients were evaluated for adverse events (all grades), serious adverse events, and any adverse events requiring drug interruption or discontinuation throughout the course of the study.

Two committees were convened to evaluate the safety of this trial, the trial steering committee (TSC) and the independent data monitoring committee (IDMC).

Background therapy: -

Evidence for comparator:

Current clinical mTOR inhibitors such as everolimus inhibit the mTORC1 complex only through an indirect mechanism that does not involve the mTOR kinase, and there is increasing evidence that this mechanism sets off a negative feedback loop leading to the activation of mTORC2, AKT phosphorylation, and ultimately treatment resistance. Preclinical studies have demonstrated that rapamycin analogues are unable to completely abrogate mTORC1 signaling and the residual activity of the downstream effector 4E-BP1 can continue to initiate protein translation. Mammalian target of rapamycin kinase inhibitors have been developed to enhance the antitumor activity through more complete TORC1 inhibition and abrogating AKT-mediated TORC2 activation.

Vistusertib (AZD2014) is a dual inhibitor of both mTORC1 and mTORC2 complexes; compared with everolimus, vistusertib has demonstrated more complete growth inhibition and cell death in vitro and in vivo based on a greater inhibitory function against mTORC1 and additional inhibition of mTORC2, especially in ER-positive breast cancer models. Most preclinical and clinical applications of PI3K inhibitors or mTOR inhibitors use continuous daily dosing schedules. However, high-dose pulsatile administration has been proposed as a way to induce more complete suppression of mTOR signaling to maximize therapeutic benefit while reducing toxic effects by allowing for recovery of nontarget tissues during dosing breaks.

Using intermittent dosing (2 days on and 5 days off), vistusertib induced rapid tumor regression in

preclinical models.

The MANTA trial evaluated whether the addition of vistusertib (AZD2014) increases PFS and other measures of antitumor activity of fulvestrant in postmenopausal women with ER-positive advanced or metastatic breast cancer who have failed prior therapy with AIs. The study also evaluated whether dual inhibition of mTORC1 and mTORC2 with vistusertib leads to improved efficacy compared with daily treatment.

Actual start date of recruitment	01 October 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Portugal: 18
Country: Number of subjects enrolled	Romania: 10
Country: Number of subjects enrolled	Spain: 55
Country: Number of subjects enrolled	United Kingdom: 152
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 40
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Georgia: 16
Worldwide total number of subjects	333
EEA total number of subjects	154

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)	193
From 65 to 84 years	136
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

430 Postmenopausal women with ER-positive, locally advanced or metastatic breast cancer were screened and were eligible if they either relapsed while undergoing or within 12 months of the end of adjuvant treatment with an AI or progressed on treatment with an AI. 97 patients screen failed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Fulvestrant Only

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.

Arm title	Fulvestrant + AZD2014 (continuous daily schedule)
------------------	---

Arm description:

Fulvestrant (C1 = D1 and D15, then day 1 of each subsequent cycle) + AZD2014 (continuous twice daily schedule)

Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.

Investigational medicinal product name	AZD2014
Investigational medicinal product code	
Other name	Vistusertib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AZD2014 was taken orally, twice daily, at a dose of 50 mg.

Arm title	Fulvestrant + AZD2014 (intermittent schedule)
------------------	---

Arm description:	
Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off)	
Arm type	Experimental
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.

Investigational medicinal product name	AZD2014
Investigational medicinal product code	
Other name	Vistusertib
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

AZD2014 was taken twice daily on days 1 and 2 over every week at a starting dose of 125mg

Arm title	Fulvestrant + everolimus
------------------	--------------------------

Arm description:

Fulvestrant and everolimus

Arm type	Active comparator
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Fulvestrant 500 mg will be administered in the clinic as two IM injections of 250mg each on Days 1 and 15 of Cycle 1 and Day 1 of each subsequent 28-day cycle.

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

Dosage and administration details:

Everolimus was taken once daily continuously (without a scheduled break) at a starting dose of 10mg

Number of subjects in period 1	Fulvestrant Only	Fulvestrant + AZD2014 (continuous daily schedule)	Fulvestrant + AZD2014 (intermittent schedule)
Started	67	103	98
Completed	66	101	95
Not completed	1	2	3
Consent withdrawn by subject	1	-	3
Physician decision	-	2	-

Number of subjects in period 1	Fulvestrant +
---------------------------------------	---------------

	everolimus
Started	65
Completed	64
Not completed	1
Consent withdrawn by subject	-
Physician decision	1

Baseline characteristics

Reporting groups

Reporting group title	Fulvestrant Only
Reporting group description: -	
Reporting group title	Fulvestrant + AZD2014 (continuous daily schedule)
Reporting group description:	
Fulvestrant (C1 = D1 and D15, then day 1 of each subsequent cycle) + AZD2014 (continuous twice daily schedule)	
Reporting group title	Fulvestrant + AZD2014 (intermittent schedule)
Reporting group description:	
Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off)	
Reporting group title	Fulvestrant + everolimus
Reporting group description:	
Fulvestrant and everolimus	

Reporting group values	Fulvestrant Only	Fulvestrant + AZD2014 (continuous daily schedule)	Fulvestrant + AZD2014 (intermittent schedule)
Number of subjects	67	103	98
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)	41	54	48
From 65-84 years	21	44	43
85 years and over	1	2	5
Not recorded	4	3	2
Gender categorical			
Units: Subjects			
Female	67	103	98
Male	0	0	0
Site of metastatic disease			
Units: Subjects			
Visceral	41	64	53
Bone Only	18	24	21
Other	7	13	21
Not recorded	1	2	3
T Stage			
T Stage of Disease at baseline			
Units: Subjects			
T1	13	22	17
T2	30	42	42

T3	6	18	12
T4	3	8	9
NK	12	10	16
Not recorded	3	3	2

Reporting group values	Fulvestrant + everolimus	Total	
Number of subjects	65	333	
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)	31	174	
From 65-84 years	28	136	
85 years and over	1	9	
Not recorded	5	14	
Gender categorical Units: Subjects			
Female	65	333	
Male	0	0	
Site of metastatic disease Units: Subjects			
Visceral	44	202	
Bone Only	11	74	
Other	9	50	
Not recorded	1	7	
T Stage			
T Stage of Disease at baseline			
Units: Subjects			
T1	15	67	
T2	27	141	
T3	7	43	
T4	4	24	
NK	7	45	
Not recorded	5	13	

End points

End points reporting groups

Reporting group title	Fulvestrant Only
Reporting group description: -	
Reporting group title	Fulvestrant + AZD2014 (continuous daily schedule)
Reporting group description: Fulvestrant (C1 = D1 and D15, then day 1 of each subsequent cycle) + AZD2014 (continuous twice daily schedule)	
Reporting group title	Fulvestrant + AZD2014 (intermittent schedule)
Reporting group description: Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off)	
Reporting group title	Fulvestrant + everolimus
Reporting group description: Fulvestrant and everolimus	

Primary: Progression Free Survival

End point title	Progression Free Survival
End point description: PFS is defined as date of randomisation to date of first documented disease progression (using RECIST v1.1) or death from any cause, whichever occurs first.	
End point type	Primary
End point timeframe: Date of randomisation to disease progression	

End point values	Fulvestrant Only	Fulvestrant + AZD2014 (continuous daily schedule)	Fulvestrant + AZD2014 (intermittent schedule)	Fulvestrant + everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	101	95	64
Units: month				
median (confidence interval 95%)	5.4 (3.5 to 9.2)	7.6 (5.9 to 9.4)	8.0 (5.6 to 9.9)	12.3 (7.7 to 15.7)

Statistical analyses

Statistical analysis title	Fulvestrant + AZD2014 (cont) vs fulvestrant alone
Statistical analysis description: Difference in PFS between patients assigned fulvestrant plus daily AZD2014 and those receiving fulvestrant alone. Performed using the unadjusted Cox model.	
Comparison groups	Fulvestrant + AZD2014 (continuous daily schedule) v Fulvestrant Only

Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.46
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.24

Statistical analysis title	Fulvestrant + AZD2014 (intermittent) vs fulvest...
-----------------------------------	--

Statistical analysis description:

Difference in PFS between patients assigned fulvestrant plus intermittent AZD2014 and those receiving fulvestrant alone. Performed using the unadjusted Cox model.

Comparison groups	Fulvestrant + AZD2014 (intermittent schedule) v Fulvestrant Only
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.12

Statistical analysis title	Fulvestrant + AZD2014 (cont) vs everolimus
-----------------------------------	--

Statistical analysis description:

PFS in patients assigned to fulvestrant + everolimus compared to fulvestrant + continuous AZD2014

Comparison groups	Fulvestrant + everolimus v Fulvestrant + AZD2014 (continuous daily schedule)
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.9

Statistical analysis title	Fulvestrant + AZD2014 (int) vs everolimus
Statistical analysis description:	
PFS in patients assigned to fulvestrant + everolimus compared to fulvestrant + intermittent AZD2014	
Comparison groups	Fulvestrant + everolimus v Fulvestrant + AZD2014 (intermittent schedule)
Number of subjects included in analysis	159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.01

Statistical analysis title	Fulvestrant alone vs fulvestrant plus everolimus
Statistical analysis description:	
PFS in patients assigned to fulvestrant + everolimus compared to fulvestrant alone	
Comparison groups	Fulvestrant + everolimus v Fulvestrant Only
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.92

Secondary: Objective Response Rate

End point title	Objective Response Rate
-----------------	-------------------------

End point description:

OR is defined as the number of patients with at least one confirmed response of CR or PR (using RECIST v1.1).

ORR is defined as the number of patients with an OR divided by the number of patients with measurable disease at baseline.

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

End point timeframe:

Baseline to response on CT scan

End point values	Fulvestrant Only	Fulvestrant + AZD2014 (continuous daily schedule)	Fulvestrant + AZD2014 (intermittent schedule)	Fulvestrant + everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	100	95	64
Units: response rate				
number (confidence interval 95%)	25.0 (14.0 to 38.9)	30.4 (20.5 to 41.8)	28.6 (18.8 to 40.0)	41.2 (27.6 to 55.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit rate

End point title	Clinical Benefit rate
-----------------	-----------------------

End point description:

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

End point timeframe:

Baseline to at least 24 weeks.

End point values	Fulvestrant Only	Fulvestrant + AZD2014 (continuous daily schedule)	Fulvestrant + AZD2014 (intermittent schedule)	Fulvestrant + everolimus
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	101	95	64
Units: percent				
number (confidence interval 95%)	38 (24.7 to 52.8)	44.7 (33.3 to 56.6)	39 (28 to 50.8)	56.9 (42.2 to 70.7)

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Date of informed consent until end of treatment or event resolution if event is unresolved at time of end of treatment

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

Dictionary used

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

Dictionary version	23
--------------------	----

Reporting groups

Reporting group title	Fulvestrant Only
-----------------------	------------------

Reporting group description: -

Reporting group title	Fulvestrant + AZD2014 (continuous daily schedule)
-----------------------	---

Reporting group description:

Fulvestrant (C1 = D1 and D15, then day 1 of each subsequent cycle) + AZD2014 (continuous twice daily schedule)

Reporting group title	Fulvestrant + AZD2014 (intermittent schedule)
-----------------------	---

Reporting group description:

Fulvestrant + AZD2014 (intermittent schedule - 2 days on, 5 days off)

Reporting group title	Fulvestrant + everolimus
-----------------------	--------------------------

Reporting group description:

Fulvestrant and everolimus

Serious adverse events	Fulvestrant Only	Fulvestrant + AZD2014 (continuous daily schedule)	Fulvestrant + AZD2014 (intermittent schedule)
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 60 (13.33%)	34 / 95 (35.79%)	24 / 91 (26.37%)
number of deaths (all causes)	51	75	70
number of deaths resulting from adverse events	1	1	2
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 60 (3.33%)	3 / 95 (3.16%)	1 / 91 (1.10%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 60 (0.00%)	5 / 95 (5.26%)	3 / 91 (3.30%)
occurrences causally related to treatment / all	0 / 0	4 / 5	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	1 / 60 (1.67%)	1 / 95 (1.05%)	4 / 91 (4.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 60 (0.00%)	4 / 95 (4.21%)	2 / 91 (2.20%)
occurrences causally related to treatment / all	0 / 0	4 / 4	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Infection			
subjects affected / exposed	2 / 60 (3.33%)	10 / 95 (10.53%)	3 / 91 (3.30%)
occurrences causally related to treatment / all	0 / 2	5 / 12	0 / 3
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0

Serious adverse events	Fulvestrant + everolimus		
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 64 (34.38%)		
number of deaths (all causes)	48		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 64 (1.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	0 / 64 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	10 / 64 (15.63%)		
occurrences causally related to treatment / all	4 / 12		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fulvestrant Only	Fulvestrant + AZD2014 (continuous daily schedule)	Fulvestrant + AZD2014 (intermittent schedule)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 60 (100.00%)	93 / 95 (97.89%)	89 / 91 (97.80%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 60 (36.67%)	46 / 95 (48.42%)	53 / 91 (58.24%)
occurrences (all)	22	46	53
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	19 / 60 (31.67%)	39 / 95 (41.05%)	68 / 91 (74.73%)
occurrences (all)	27	65	153
Infection			
subjects affected / exposed	23 / 60 (38.33%)	35 / 95 (36.84%)	35 / 91 (38.46%)
occurrences (all)	30	58	70
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	4 / 60 (6.67%)	51 / 95 (53.68%)	23 / 91 (25.27%)
occurrences (all)	4	113	43
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	25 / 60 (41.67%)	40 / 95 (42.11%)	41 / 91 (45.05%)
occurrences (all)	47	73	97

Non-serious adverse events	Fulvestrant +		
-----------------------------------	---------------	--	--

	everolimus		
Total subjects affected by non-serious adverse events subjects affected / exposed	63 / 64 (98.44%)		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	40 / 64 (62.50%) 40		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) Infection subjects affected / exposed occurrences (all)	27 / 64 (42.19%) 40 29 / 64 (45.31%) 74		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	34 / 64 (53.13%) 48		
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	28 / 64 (43.75%) 57		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 January 2014	<ul style="list-style-type: none">- Addition of new sites- Changes to Principle Investigators included in the original application- Administrative changes to protocol
20 March 2014	<ul style="list-style-type: none">- Protocol and patient documentation amended to include a 4th treatment arm – Fulvestrant + AZD2014 125mg intermittent schedule- CTA amended- AZD2014 labels amended – submitted as booklet
15 December 2014	<ul style="list-style-type: none">- AZD2014 Investigator's Brochure (IB) - reference safety information updated.- Faslodex (Fulvestrant) SmPC submitted
17 March 2016	<ul style="list-style-type: none">- Change of sponsor representative- Addition of 5 countries- Administrative clarifications- Removal of DLCO and reduction in frequency of ECGs- Interim analysis details updated
22 May 2017	<ul style="list-style-type: none">- Changes in IB to Edition 7.
13 December 2018	<ul style="list-style-type: none">- Change in IB to Edition 8
08 February 2019	<ul style="list-style-type: none">- UK, Spain, Hungary, France and Romania addition of Fisher Clinical Services GmbH as a manufacturer (QP release) and importer for the IMP, AZD2014 and non-IMP Fulvestrant as contingency in case of a no-deal Brexit.
21 November 2019	<ul style="list-style-type: none">- Change in AZD2014 IB to Edition 9- Everolimus SmPC non-substantial update (date of revision of the text 02Apr2019)
19 May 2020	<ul style="list-style-type: none">- Change in AZD2014 IB to Edition 10.
16 December 2021	<ul style="list-style-type: none">- Substantial amendment for notification – to inform MHRA and REC regarding the end of trial plan for the MANTA trial and subsequent timeline for end of trial submission (early termination).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31465093>

