



Clinical trial results:

Fulvestrant with or without AZD6244, a mitogen-activated protein kinase kinase (MEK) 1/2 inhibitor, in advanced stage breast cancer progressing after aromatase inhibitor: a randomized placebo-controlled double-blind phase II trial.

Summary

EudraCT number	2010-019965-27
Trial protocol	BE
Global end of trial date	08 September 2016

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	SAKK21/08
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01160718
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research, +41 31389 91 91, sakkcc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research, +41 31389 91 91, sakkcc@sakk.ch

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	12 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 September 2016
Global end of trial reached?	Yes
Global end of trial date	08 September 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial is to assess the efficacy of the combination AZD6244-fulvestrant in patients with endocrine sensitive breast cancer progressing after aromatase inhibitors.

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continuous assessment of laboratory values and vital signs.

Background therapy:

All patients received Fulvestrant 500mg i.m. on day 1, day 15 and day 1 of cycle 2 then every 28 +/- 3 days.

Evidence for comparator:

A placebo-controlled study design was chosen to test the effect of AZD6244 when provided in combination with Fulvestrant.

Actual start date of recruitment	10 November 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Switzerland: 32
Country: Number of subjects enrolled	Belgium: 14
Worldwide total number of subjects	46
EEA total number of subjects	14

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)	22
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

89 patients were planned to be enrolled. The trial was prematurely closed for accrual following the interim analysis as defined in the protocol after the inclusion of 46 patients. 14 patients had been enrolled in Belgium (1 center) and 32 patients in Switzerland (19 centres). First patient was enrolled on 18-Nov-2010.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fulfils all inclusion criteria and not any of the exclusion criteria, he/she was randomized.

Period 1

Period 1 title	Randomization
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Fulvestrat + AZD6244

Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.

Arm type	Experimental
Investigational medicinal product name	AZD6244
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg (3 capsules of 25 mg) twice daily (150 mg per day), p.o.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

Arm title	B: Fulvestrat + Placebo
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Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Arm type	Placebo
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Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

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

Dosage and administration details:

Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Number of subjects in period 1	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo
Started	23	23
Completed	23	22
Not completed	0	1
No treatment received	-	1

Period 2

Period 2 title	Baseline (Safety)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Fulvestrat + AZD6244

Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.

Arm type	Experimental
Investigational medicinal product name	AZD6244
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg (3 capsules of 25 mg) twice daily (150 mg per day), p.o.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

Arm title	B: Fulvestrat + Placebo
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Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Arm type	Placebo
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

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

Dosage and administration details:

Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Number of subjects in period 2	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo
Started	23	22
Completed	22	20
Not completed	1	2
Major eligibility criteria not met (posteriori)	1	2

Period 3

Period 3 title	Baseline (ITT)
Is this the baseline period?	Yes ^[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
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Arm title	A: Fulvestrat + AZD6244
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Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.

Arm type	Experimental
Investigational medicinal product name	AZD6244
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg (3 capsules of 25 mg) twice daily (150 mg per day), p.o.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

Arm title	B: Fulvestrat + Placebo
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Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Arm type	Placebo
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

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

Dosage and administration details:

Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Notes:

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

Justification: A randomization and baseline period had to be prepended, as one patient in the Placebo arm did not receive study medication (randomization period) and baseline data were assessed for the ITT analysis set which is different from the safety analysis set (baseline period).

Number of subjects in period 3 ^[2]	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo
Started	22	20
Completed	22	20

Notes:

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

Justification: Baseline data were assessed for the ITT population which is different from the total number on enrolled patients. The ITT population excluded one randomized patient that did not receive study medication and three patients that posteriori did not satisfy major eligibility criteria and were excluded from the analysis set.

Period 4

Period 4 title	Treatment (ITT)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Fulvestrat + AZD6244

Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.

Arm type	Experimental
Investigational medicinal product name	AZD6244
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg (3 capsules of 25 mg) twice daily (150 mg per day), p.o.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

Arm title	B: Fulvestrat + Placebo
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Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Arm type	Placebo
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Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

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

Dosage and administration details:

Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Number of subjects in period 4	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo
Started	22	20
Completed	22	20

Period 5

Period 5 title	Follow-up (ITT)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	A: Fulvestrat + AZD6244

Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.

Arm type	Experimental
Investigational medicinal product name	AZD6244
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

75 mg (3 capsules of 25 mg) twice daily (150 mg per day), p.o.

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

Arm title	B: Fulvestrat + Placebo
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Arm description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Arm type	Placebo
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days

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

Dosage and administration details:

Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Number of subjects in period 5	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo
Started	22	20
Completed	6	5
Not completed	16	15
Death (non AE related)	16	15

Baseline characteristics

Reporting groups

Reporting group title	A: Fulvestrat + AZD6244
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Reporting group description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.

Reporting group title	B: Fulvestrat + Placebo
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Reporting group description:

Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally

Reporting group values	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo	Total
Number of subjects	22	20	42
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Baseline data were assessed for the ITT population.			
Units: years			
median	65.5	69.0	
full range (min-max)	40.0 to 79.0	46.0 to 79.0	-
Gender categorical			
Baseline data were assessed for the ITT population.			
Units: Subjects			
Female	22	20	42
Male	0	0	0

End points

End points reporting groups

Reporting group title	A: Fulvestrat + AZD6244
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.	
Reporting group title	B: Fulvestrat + Placebo
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally	
Reporting group title	A: Fulvestrat + AZD6244
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.	
Reporting group title	B: Fulvestrat + Placebo
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally	
Reporting group title	A: Fulvestrat + AZD6244
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.	
Reporting group title	B: Fulvestrat + Placebo
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally	
Reporting group title	A: Fulvestrat + AZD6244
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.	
Reporting group title	B: Fulvestrat + Placebo
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally	
Reporting group title	A: Fulvestrat + AZD6244
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.	
Reporting group title	B: Fulvestrat + Placebo
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally	
Reporting group title	A: Fulvestrat + AZD6244
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + AZD6244, 75 mg (3 capsules of 25 mg) twice daily (150 mg per day), taken orally.	
Reporting group title	B: Fulvestrat + Placebo
Reporting group description: Fulvestrant, 500 mg as intramuscular injection on day 1, on day 15, on day 1 of cycle 2, and then every 28 +/- 3 days + Placebo (3 capsules, same appearance as AZD6244) twice daily, taken orally	
Subject analysis set title	Duration of response
Subject analysis set type	Intention-to-treat
Subject analysis set description: Patients rreaching CR or PR	

Primary: Primary Endpoint - Disease control

End point title	Primary Endpoint - Disease control ^[1]
End point description:	Disease control defined as the sum of CR + PR + stable disease $\geq$ 24 weeks, according to RECIST 1.1
End point type	Primary
End point timeframe:	24 weeks

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: As the study has been terminated prematurely and the number of enrolled patients was reduced, statistical hypothesis testing on the primary endpoint was waived.

End point values	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: Percentage (Pts with CR, PR or SD $\geq$ 24 w.)				
number (confidence interval 95%)	23 (8 to 45)	50 (27 to 73)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint - Overall response

End point title	Secondary endpoint - Overall response
End point description:	The best overall response (i.e. CR or PR) is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In the case of stable disease, measurements must have met the SD criteria at least once after trial entry at a minimum interval of [6 to 8 weeks].
End point type	Secondary
End point timeframe:	From treatment initiation until disease progression/recurrence

End point values	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	20		
Units: Percentage (Pts with CR or PR)				
number (confidence interval 95%)	5 (0 to 23)	15 (3 to 38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint - Time to treatment failure (TTF)

End point title	Secondary endpoint - Time to treatment failure (TTF)
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End point description:

Time to treatment failure was calculated from randomization until discontinuation of all trial treatment due to any reason (e.g. progressive disease, toxicity, refusal, death).

End point type	Secondary
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End point timeframe:

From randomization until discontinuation of the trial treatment.

End point values	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[2]	20 ^[3]		
Units: TTF (months)				
median (confidence interval 95%)	5.1 (2.3 to 6.7)	5.6 (3.4 to 10.2)		

Notes:

[2] - 22 patients with events | 0 patients censored

[3] - 20 patients with events | 0 patients censored

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint - Time to AZD6244 discontinuation

End point title	Secondary endpoint - Time to AZD6244 discontinuation
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End point description:

Time to AZD6244 discontinuation will be calculated from randomization to discontinuation of AZD6244 treatment due to any reason (e.g. progressive disease, toxicity, refusal, death).

End point type	Secondary
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End point timeframe:

From randomization until discontinuation of AZD6244 treatment.

End point values	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[4]	20 ^[5]		
Units: Months				
median (confidence interval 95%)	2.7 (1.2 to 5.7)	5.5 (3.4 to 8.4)		

Notes:

[4] - 22 patients with events | 0 patients censored

[5] - 20 patients with events | 0 patients censored

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint - Duration of response

End point title	Secondary endpoint - Duration of response
End point description: Duration of overall response (CR+PR) was calculated from the time that measurement criteria were met for the first time until documented tumor progression. Second-line treatment started before documented progression was not allowed. If done nevertheless, the duration of overall response was censored at the time when the second-line treatment was initiated.	
End point type	Secondary
End point timeframe: Duration of overall response (CR+PR) was calculated from the time that measurement criteria were met for the first time until documented tumor progression.	

End point values	Duration of response			
Subject group type	Subject analysis set			
Number of subjects analysed	4			
Units: Days				
number (not applicable)				
Arm A: Patient 21 (censored, EoT)	1222			
Arm B: Patient 19 (event)	932			
Arm B: Patient 28 (censored, withdrawal of IC)	51			
Arm B: Patient 30 (event)	197			

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary Endpoint - Progression free survival (PFS)

End point title	Secondary Endpoint - Progression free survival (PFS)
End point description: Progression-free survival was calculated from randomization until documented tumor progression or death, whichever occurred first. The start of a new line of anticancer treatment was not allowed before documented progression. If done nevertheless, progression-free survival for these patients was censored at the time when the new line of treatment was initiated.	
End point type	Secondary
End point timeframe: Time from randomization until disease progression or death.	

End point values	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[6]	20 ^[7]		
Units: PFS (month)				
median (confidence interval 95%)	3.7 (1.9 to 5.8)	5.6 (3.4 to 13.6)		

Notes:

[6] - 20 patients with progression | 2 patients censored

[7] - 17 patients with progression | 3 patients censored

Statistical analyses

No statistical analyses for this end point

Secondary: Secondary endpoint - Overall survival

End point title	Secondary endpoint - Overall survival
End point description:	
End point type	Secondary
End point timeframe:	
Time from randomization until death.	

End point values	A: Fulvestrat + AZD6244	B: Fulvestrat + Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22 ^[8]	20 ^[9]		
Units: OS (months)				
median (confidence interval 95%)	30.6 (16.1 to 36.1)	31.7 (15.2 to 45.8)		

Notes:

[8] - 16 patients with death | 6 patients censored

[9] - 15 patients with death | 5 patients censored

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From inclusion until end-of-treatment visit (max. 5 weeks after end of treatment)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Arm A: Safety Set
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Reporting group description: -

Reporting group title	Arm B: Safety Set
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Reporting group description: -

Serious adverse events	Arm A: Safety Set	Arm B: Safety Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 23 (21.74%)	7 / 22 (31.82%)	
number of deaths (all causes)	17	15	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acetabulum fracture			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			

subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Large intestinal obstruction			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			

subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A: Safety Set	Arm B: Safety Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 23 (100.00%)	22 / 22 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Tumour pain			
subjects affected / exposed	2 / 23 (8.70%)	3 / 22 (13.64%)	
occurrences (all)	2	3	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 23 (4.35%)	9 / 22 (40.91%)	
occurrences (all)	1	10	
Hypertension			
subjects affected / exposed	11 / 23 (47.83%)	12 / 22 (54.55%)	
occurrences (all)	11	17	

Lymphoedema			
subjects affected / exposed	5 / 23 (21.74%)	2 / 22 (9.09%)	
occurrences (all)	6	4	
Peripheral ischaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Angiopathy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	0 / 23 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Face oedema			
subjects affected / exposed	5 / 23 (21.74%)	0 / 22 (0.00%)	
occurrences (all)	6	0	
Oedema peripheral			
subjects affected / exposed	7 / 23 (30.43%)	4 / 22 (18.18%)	
occurrences (all)	14	6	
Fatigue			
subjects affected / exposed	13 / 23 (56.52%)	11 / 22 (50.00%)	
occurrences (all)	18	15	
Pyrexia			
subjects affected / exposed	1 / 23 (4.35%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Influenza like illness			
subjects affected / exposed	2 / 23 (8.70%)	1 / 22 (4.55%)	
occurrences (all)	2	2	
Ill-defined disorder			
subjects affected / exposed	3 / 23 (13.04%)	1 / 22 (4.55%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	4 / 23 (17.39%)	6 / 22 (27.27%)	
occurrences (all)	4	7	
Reproductive system and breast disorders			

Pelvic pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 23 (30.43%)	9 / 22 (40.91%)	
occurrences (all)	8	11	
Dyspnoea			
subjects affected / exposed	4 / 23 (17.39%)	6 / 22 (27.27%)	
occurrences (all)	6	6	
Epistaxis			
subjects affected / exposed	2 / 23 (8.70%)	1 / 22 (4.55%)	
occurrences (all)	2	1	
Nasal congestion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Pneumothorax			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Upper-airway cough syndrome			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Respiratory failure			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Respiratory disorder			
subjects affected / exposed	2 / 23 (8.70%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Psychiatric disorders			

Depression subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 22 (4.55%) 1	
Insomnia subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 22 (9.09%) 4	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 2	0 / 22 (0.00%) 0	
Blood alkaline phosphatase increased subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 22 (0.00%) 0	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Investigation subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Weight increased subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	2 / 22 (9.09%) 4	
Weight decreased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 22 (4.55%) 1	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Fracture subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Hip fracture subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Recall phenomenon			

subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Angina pectoris			
subjects affected / exposed	1 / 23 (4.35%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Palpitations			
subjects affected / exposed	3 / 23 (13.04%)	0 / 22 (0.00%)	
occurrences (all)	3	0	
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Depressed level of consciousness			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	1 / 23 (4.35%)	3 / 22 (13.64%)	
occurrences (all)	1	4	
Dysaesthesia			
subjects affected / exposed	1 / 23 (4.35%)	4 / 22 (18.18%)	
occurrences (all)	1	4	
Dysgeusia			
subjects affected / exposed	2 / 23 (8.70%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Headache			
subjects affected / exposed	3 / 23 (13.04%)	6 / 22 (27.27%)	
occurrences (all)	3	13	
Memory impairment			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			

subjects affected / exposed occurrences (all)	5 / 23 (21.74%) 5	4 / 22 (18.18%) 5	
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 4	3 / 22 (13.64%) 3	
Syncope subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 22 (0.00%) 0	
Tremor subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Ear and labyrinth disorders Hypoacusis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Tinnitus subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Vertigo subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Eye disorders Vision blurred subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	2 / 22 (9.09%) 2	
Cataract subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 22 (4.55%) 2	
Dry eye subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	3 / 22 (13.64%) 6	
Eye disorder subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 4	1 / 22 (4.55%) 1	
Photophobia			

subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Retinopathy subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Periorbital oedema subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 4	2 / 22 (9.09%) 2	
Ascites subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Colitis subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Constipation subjects affected / exposed occurrences (all)	6 / 23 (26.09%) 7	7 / 22 (31.82%) 8	
Dental caries subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 2	
Diarrhoea subjects affected / exposed occurrences (all)	12 / 23 (52.17%) 14	8 / 22 (36.36%) 8	
Dry mouth subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 5	0 / 22 (0.00%) 0	
Duodenal hemorrhage subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	

Dyspepsia		
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	1
Dysphagia		
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	1
Gastrointestinal disorder		
subjects affected / exposed	2 / 23 (8.70%)	0 / 22 (0.00%)
occurrences (all)	3	0
Gingival pain		
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	1
Haemorrhoids		
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	1	0
Stomatitis		
subjects affected / exposed	4 / 23 (17.39%)	1 / 22 (4.55%)
occurrences (all)	4	1
Nausea		
subjects affected / exposed	9 / 23 (39.13%)	10 / 22 (45.45%)
occurrences (all)	10	11
Oral dysaesthesia		
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	1	0
Periodontal disease		
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	1	0
Salivary duct inflammation		
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)
occurrences (all)	1	0
Enteritis		
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)
occurrences (all)	0	2
Abdominal pain upper		
subjects affected / exposed	2 / 23 (8.70%)	2 / 22 (9.09%)
occurrences (all)	2	2

Vomiting subjects affected / exposed occurrences (all)	8 / 23 (34.78%) 9	5 / 22 (22.73%) 9	
Hepatobiliary disorders Portal vein thrombosis subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 4	2 / 22 (9.09%) 2	
Dry skin subjects affected / exposed occurrences (all)	5 / 23 (21.74%) 5	1 / 22 (4.55%) 1	
Erythema multiforme subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	1 / 22 (4.55%) 1	
Onychomadesis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Nail ridging subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all)	2 / 23 (8.70%) 2	0 / 22 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	3 / 22 (13.64%) 3	
Dermatitis acneiform subjects affected / exposed occurrences (all)	12 / 23 (52.17%) 16	2 / 22 (9.09%) 2	
Rash maculo-papular subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 4	0 / 22 (0.00%) 0	
Skin disorder			

subjects affected / exposed occurrences (all)	7 / 23 (30.43%) 8	1 / 22 (4.55%) 1	
Skin ulcer subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	1 / 22 (4.55%) 1	
Renal and urinary disorders Cystitis noninfective subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 23 (17.39%) 5	5 / 22 (22.73%) 11	
Arthritis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 1	
Back pain subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 6	4 / 22 (18.18%) 9	
Bone pain subjects affected / exposed occurrences (all)	3 / 23 (13.04%) 3	7 / 22 (31.82%) 11	
Flank pain subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Muscular weakness subjects affected / exposed occurrences (all)	1 / 23 (4.35%) 1	0 / 22 (0.00%) 0	
Kyphosis subjects affected / exposed occurrences (all)	0 / 23 (0.00%) 0	1 / 22 (4.55%) 3	
Musculoskeletal disorder			

subjects affected / exposed	7 / 23 (30.43%)	1 / 22 (4.55%)	
occurrences (all)	8	1	
Myalgia			
subjects affected / exposed	4 / 23 (17.39%)	4 / 22 (18.18%)	
occurrences (all)	8	7	
Myositis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	1 / 23 (4.35%)	1 / 22 (4.55%)	
occurrences (all)	1	1	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Osteoporosis			
subjects affected / exposed	1 / 23 (4.35%)	2 / 22 (9.09%)	
occurrences (all)	1	2	
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	5 / 22 (22.73%)	
occurrences (all)	1	6	
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 23 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	3	
Bronchitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	4 / 23 (17.39%)	1 / 22 (4.55%)	
occurrences (all)	6	1	
Lung infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	
Lymph gland infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	2	0	

Nail infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	2	
Paronychia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	0 / 23 (0.00%)	4 / 22 (18.18%)	
occurrences (all)	0	4	
Skin infection			
subjects affected / exposed	2 / 23 (8.70%)	0 / 22 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	0 / 23 (0.00%)	2 / 22 (9.09%)	
occurrences (all)	0	2	
Vaginal infection			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 23 (26.09%)	3 / 22 (13.64%)	
occurrences (all)	6	3	
Hypoglycaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Obesity			
subjects affected / exposed	0 / 23 (0.00%)	1 / 22 (4.55%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 July 2010	Adaptations were made regarding the collection of information about available tumor tissue and the safety section has been changed by listing only adverse events which were considered as related to AZD6244.
02 February 2011	Eligibility criteria were clarified and especially not only patients with measurable disease or bone-only disease were eligible but also patients with assessable unequivocal small liver or lung metastases.
15 September 2011	Following the interim safety analysis, Amendment 3 was issued in order to adapt the definition of dose modification of AZD6244/placebo: it was advised to proceed to a dose reduction as soon as AEs of grade 2 appear, instead of upon appearance of AEs of grade 3 or higher.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported