Clinical trial results:
A randomised Phase II study of Enzalutamide (MDV3100) in combination with AZD5363 in Patients with Metastatic Castration - Resistant Prostate Cancer

Summary

EudraCT number	2013-004091-34
Trial protocol	GB
Global end of trial date	07 November 2022

Results information

Result version number	v1 (current)
This version publication date	24 November 2023
First version publication date	24 November 2023

Trial information

Trial identification

Sponsor protocol code	CCR3972

Additional study identifiers

ISRCTN number	ISRCTN17168679
ClinicalTrials.gov id (NCT number)	NCT02525068
WHO universal trial number (UTN)	-
Other trial identifiers	ICR-CTSU number: lCR-CTSU/2012/10037, Cancer Research UK Reference Number: CRUKE/12/050, REC reference number: 14/LO/0259

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research
Sponsor organisation address	15 Cotswold Road, Sutton, London, United Kingdom, SM2 5NG
Public contact	Alexa Gillman, The Institute of Cancer Research, 44 02087224188, RE-AKT-icrctsu@icr.ac.uk
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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	07 April 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 April 2022
Global end of trial reached?	Yes
Global end of trial date	07 November 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I safety run in
To find out how safe and how well tolerated the combination treatment of enzalutamide and AZD5363 is.
To estimate the maximum dose of AZD5363 that is tolerated in combination with enzalutamide.
To identify the dose of AZD5363 to use in the combination treatment in the randomised phase II trial.

Randomised phase II
To measure the response to AZD5363 + enzalutamide and placebo + enzalutamide.
To compare the responses to AZD5363 + enzalutamide and placebo + enzalutamide.

Single stage phase II expansion cohort
To measure the response to AZD5363 + enzalutamide in patients who have previously progressed on enzalutamide alone

Protection of trial subjects:

For trial entry and optional tissue donation, patients were given a verbal explanation, discussion and written information. The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient. Eligible patients were given as much time as they needed to consider, ask questions and come to a decision about entering the trial, prior to giving consent for entering the trial. The patient information sheet described which parties would have access to their identifiable personal information and patients were asked to give consent to this. The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.

Background therapy:

Prostate adenocarcinoma is the most common malignancy affecting men in the Western world, with over 570,000 new cases annually and an estimated 94, 000 deaths in Europe in 2008 and 32,050 deaths in the United States. Up to 40% of men initially diagnosed with localized prostate cancer will eventually develop metastases. In patients with advanced disease, androgen deprivation with either orchiectomy or medical castration with GnRH agonists is highly effective in shrinking tumour burden, decreasing prostate-specific antigen (PSA) levels, and enhancing quality of life. However, nearly all patients experience disease progression following hormonal manipulations, and develop castration-resistant prostate cancer (CRPC). Mitoxantrone was the first chemotherapy to show a palliative benefit for patients with CRPC, and was subsequently approved by the US Food and Drug Administration (FDA). In 2003, the TAX327 trial showed, for CRPC patients treated with 3 weekly docetaxel had a survival advantage over mitoxantrone (OS: 19.2 mo. vs. 16.3 mo., p = 0.009). Until recently, cytotoxic chemotherapy had been the only therapy shown to improve survival for patients with CRPC. In the last five years, five novel treatments have shown survival gains in phase III trials, including sipuleucel-T abiraterone acetate, alpharadin, cabazitaxel and enzalutamide.

Evidence for comparator:

Recent preclinical data suggest that reciprocal crosstalk between the AR and PI3K/AKT signalling pathways occur in PTEN-deficient CRPC. Specifically, activation of the PI3K / AKT pathway can be associated with decreased androgen receptor signalling, and inhibition of the PI3K / AKT pathway increases AR signalling in PTEN-deficient prostate cancer cells. Proposed mechanisms to account for these observations include PI3K / AKT pathway inhibition resulting in feedback activation of AR via the up regulation of HER kinases, while inhibition of AR relieves feedback inhibition of AKT by the phosphatase PHLPP. Such reciprocal cooperativity between PI3K / AKT and AR pathways suggests that the inhibition of either one pathway, without the other, would lead to the achievement of sub-optimal

clinical efficacy. Carver and co-workers actually showed that the simultaneous pharmacological inhibition of the PI3K/mTOR pathway and AR caused near complete prostate cancer regression in PTEN-deficient prostate cancer preclinical mouse models. Therefore, the combined inhibition of the AR and PIK3/AKT pathways may result in more complete
inhibition of tumour cell viability and potentially more durable clinical benefit in patients with CRPC .

Actual start date of recruitment	17 December 2014
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	United Kingdom: 138
Worldwide total number of subjects	138
EEA total number of subjects	0

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)	31
From 65 to 84 years	106
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Phase I: between 12/2014 and 4/2016 16 patients were enrolled from 1 UK site
Phase II randomised: between 6/2016 and 11/2019 100 patients were enrolled from 15 UK sites
Phase II expansion: between 6/2016 and 5/2018 22 patients were enrolled from 3 UK sites

Pre-assignment

Screening details:

Patients that met the eligibility criteria were recruited into the study. Eligible patients had previous diagnosed, histologically confirmed adenocarcinoma of metastatic castration-resistant prostate cancer (mCRPC) with tumour tissue accessible for research analyses for the trial.

Period 1

Period 1 title	RE-AKT trial overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase I Safety run-in

Arm description:

This phase is to identify the safety and tolerability of enzalutamide and AZD5363 when given in a combination of once daily enzalutamide (MDV3100) with twice daily AZD5363 administered in a four days on and three days off regimen. And, to identify dose-limiting toxicities (DLTs), estimate the maximum tolerated dose (MTD) and identify a recommended Phase II dose (RP2D) of AZD5363 administered in combination with enzalutamide 160mg daily

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

Dosage and administration details:

160mg once a day

Investigational medicinal product name	AZD5363
Investigational medicinal product code	
Other name	Capivasertib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dose escalation:
Level 1 - 320mg BID 4 days on, three days off
Level 2 - 400mg BID 4 days on, three days off
Level 3 - 480mg BID 4 days on, three days off

Arm title	Phase II Expansion

Arm description:

Enzalutamide and AZD5363 in patients with previous progression on enzalutamide to explore whether the addition of AZD5363 to enzalutamide can reverse resistance

Arm type	Experimental

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

Dosage and administration details:

160mg once a day

Investigational medicinal product name	AZD5363
Investigational medicinal product code	
Other name	Capivasertib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

400mg BID 4 days on, three days off

Arm title	Phase II Randomised (AZD5363)

Arm description:

A randomised, double blind phase II trial of enzalutamide in combination with AZD5363 versus enzalutamide alone will determine if the antitumour activity of the combination therapy is superior to the antitumour activity to enzalutamide alone (enzalutamide + AZD5363 vs. enzalutamide + placebo).

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

Dosage and administration details:

160mg once a day

Investigational medicinal product name	AZD5363
Investigational medicinal product code	
Other name	Capivasertib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

400mg BID 4 days on, three days off

Arm title	Phase II Randomised (Placebo)

Arm description:

A randomised, double blind phase II trial of enzalutamide in combination with AZD5363 versus enzalutamide alone will determine if the antitumour activity of the combination therapy is superior to the antitumour activity to enzalutamide alone (enzalutamide + AZD5363 vs. enzalutamide + placebo).

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

Dosage and administration details:

160mg once a day

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

Dosage and administration details:
Placebo BID 4 days on, 3 days off

Number of subjects in period 1	Phase I Safety run-in	Phase II Expansion	Phase II Randomised (AZD5363)
Started	16	22	50
Completed	16	13	50
Not completed	0	9	0
Patients progressed on pre-combination enzalutamid	-	9	-

Number of subjects in period 1	Phase II Randomised (Placebo)
Started	50
Completed	50
Not completed	0
Patients progressed on pre-combination enzalutamid	-

Baseline characteristics

Reporting groups	
Reporting group title	Phase I Safety run-in
Reporting group description:	
This phase is to identify the safety and tolerability of enzalutamide and AZD5363 when given in a combination of once daily enzalutamide (MDV3100) with twice daily AZD5363 administered in a four days on and three days off regimen. And, to identify dose-limiting toxicities (DLTs), estimate the maximum tolerated dose (MTD) and identify a recommended Phase II dose (RP2D) of AZD5363 administered in combination with enzalutamide 160mg daily	
Reporting group title	Phase II Expansion
Reporting group description:	
Enzalutamide and AZD5363 in patients with previous progression on enzalutamide to explore whether the addition of AZD5363 to enzalutamide can reverse resistance	
Reporting group title	Phase II Randomised (AZD5363)
Reporting group description:	
A randomised, double blind phase II trial of enzalutamide in combination with AZD5363 versus enzalutamide alone will determine if the antitumour activity of the combination therapy is superior to the antitumour activity to enzalutamide alone (enzalutamide + AZD5363 vs. enzalutamide + placebo).	
Reporting group title	Phase II Randomised (Placebo)
Reporting group description:	
A randomised, double blind phase II trial of enzalutamide in combination with AZD5363 versus enzalutamide alone will determine if the antitumour activity of the combination therapy is superior to the antitumour activity to enzalutamide alone (enzalutamide + AZD5363 vs. enzalutamide + placebo).	

Reporting group values	Phase I Safety run-in	Phase II Expansion	Phase II Randomised (AZD5363)
Number of subjects	16	22	50
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	70.4	65.4	72.3
inter-quartile range (Q1-Q3)	68 to 72.6	61.9 to 73.2	67.5 to 77.9
Gender categorical Units: Subjects			
Female	0	0	0
Male	16	22	50
Disease status at trial entry			
Disease status presented at trial entry			
Units: Subjects			

Measurable soft-tissue disease (+/- bone lesions)	10	15	31
Non-measurable soft-tissue (+/- bone lesions)	3	4	10
Bone lesions only	3	3	9
Not recorded	0	0	0
Time since histological confirmation of prostate cancer			
Time since confirmation of castrate resistant disease (years) presented as median (IQR)			
Units: Years			
median	6.0	6.3	6.7
inter-quartile range (Q1-Q3)	2.6 to 9.2	3.0 to 13.9	4.2 to 11.1
Time since confirmation of castrate resistant disease			
Time since confirmation of castrate resistant disease (years), presented as median (IQR)			
Units: Years			
median	4.9	2.7	3.7
inter-quartile range (Q1-Q3)	3.6 to 6.3	1.7 to 4.4	2.4 to 5.4
PSA at trial entry			
PSA at trial entry (ng/ml) – median (Q1-Q3)			
Units: ng/ml			
median	162	35.1	144.2
inter-quartile range (Q1-Q3)	27.3 to 766	11.0 to 91.0	60 to 240.3

Reporting group values	Phase II Randomised (Placebo)	Total	
Number of subjects	50	138	
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			
Units: years			
median	71.5		
inter-quartile range (Q1-Q3)	67.7 to 76.2	-	
Gender categorical			
Units: Subjects			
Female	0	0	
Male	50	138	
Disease status at trial entry			
Disease status presented at trial entry			
Units: Subjects			
Measurable soft-tissue disease (+/- bone lesions)	25	81	

Non-measurable soft-tissue (+/- bone lesions)	8	25	
Bone lesions only	17	32	
Not recorded	0	0	
Time since histological confirmation of prostate cancer			
Time since confirmation of castrate resistant disease (years) presented as median (IQR)			
Units: Years			
median	5.9		
inter-quartile range (Q1-Q3)	2.9 to 8.7	-	
Time since confirmation of castrate resistant disease			
Time since confirmation of castrate resistant disease (years), presented as median (IQR)			
Units: Years			
median	3.7		
inter-quartile range (Q1-Q3)	2.6 to 5.4	-	
PSA at trial entry			
PSA at trial entry (ng/ml) – median (Q1-Q3)			
Units: ng/ml			
median	245		
inter-quartile range (Q1-Q3)	79.3 to 591	-	

Subject analysis sets

Subject analysis set title	Evaluable - randomised phase 2 - AZD5363
Subject analysis set type	Per protocol
Subject analysis set description:	
Evaluable population for randomised phase 2 - experimental arm - evaluable for primary endpoint overall response	
Subject analysis set title	Evaluable - randomised phase 2 - placebo
Subject analysis set type	Per protocol
Subject analysis set description:	
Evaluable population for randomised phase 2 - placebo arm - evaluable for primary endpoint overall response	
Subject analysis set title	Phase I - Dose level 1 - 320mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients allocated to dose elevel 1 of dose-fiding phase I	
Subject analysis set title	Phase I - Dose level 2 - 480mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients allocated to dose elevel 2 of dose-fiding phase I	
Subject analysis set title	Phase I - Dose level 1A - 400mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients allocated to dose elevel 1A of dose-fiding phase I	

Reporting group values	Evaluable - randomised phase 2 - AZD5363	Evaluable - randomised phase 2 - placebo	Phase I - Dose level 1 - 320mg
Number of subjects	47	48	3
Age categorical			
Units: Subjects			
In utero			

Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	72.3	71.5	67.7
inter-quartile range (Q1-Q3)	67.4 to 77.9	68.0 to 75.7	66.3 to 74.1
Gender categorical Units: Subjects			
Female	0	0	0
Male	47	48	3
Disease status at trial entry			
Disease status presented at trial entry			
Units: Subjects			
Measurable soft-tissue disease (+/- bone lesions) Non-measurable soft-tissue (+/- bone lesions) Bone lesions only Not recorded			
Time since histological confirmation of prostate cancer			
Time since confirmation of castrate resistant disease (years) presented as median (IQR)			
Units: Years median inter-quartile range (Q1-Q3)			
Time since confirmation of castrate resistant disease			
Time since confirmation of castrate resistant disease (years), presented as median (IQR)			
Units: Years median inter-quartile range (Q1-Q3)			
PSA at trial entry			
PSA at trial entry (ng/ml) – median (Q1-Q3)			
Units: ng/ml median inter-quartile range (Q1-Q3)			

Reporting group values	Phase I - Dose level 2 - 480mg	Phase I - Dose level 1A - 400mg	
Number of subjects	6	7	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years median inter-quartile range (Q1-Q3)	 68.5 68.2 to 70.7	 73.0 70.8 to 75.2	
Gender categorical Units: Subjects			
Female Male	0 6	0 7	
Disease status at trial entry			
Disease status presented at trial entry			
Units: Subjects			
Measurable soft-tissue disease (+/- bone lesions) Non-measurable soft-tissue (+/- bone lesions) Bone lesions only Not recorded			
Time since histological confirmation of prostate cancer			
Time since confirmation of castrate resistant disease (years) presented as median (IQR)			
Units: Years median inter-quartile range (Q1-Q3)			
Time since confirmation of castrate resistant disease			
Time since confirmation of castrate resistant disease (years), presented as median (IQR)			
Units: Years median inter-quartile range (Q1-Q3)			
PSA at trial entry			
PSA at trial entry (ng/ml) – median (Q1-Q3)			
Units: ng/ml median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Phase I Safety run-in

Reporting group description:

This phase is to identify the safety and tolerability of enzalutamide and AZD5363 when given in a combination of once daily enzalutamide (MDV3100) with twice daily AZD5363 administered in a four days on and three days off regimen. And, to identify dose-limiting toxicities (DLTs), estimate the maximum tolerated dose (MTD) and identify a recommended Phase II dose (RP2D) of AZD5363 administered in combination with enzalutamide 160mg daily

Reporting group title	Phase II Expansion

Reporting group description:

Enzalutamide and AZD5363 in patients with previous progression on enzalutamide to explore whether the addition of AZD5363 to enzalutamide can reverse resistance

Reporting group title	Phase II Randomised (AZD5363)

Reporting group description:

A randomised, double blind phase II trial of enzalutamide in combination with AZD5363 versus enzalutamide alone will determine if the antitumour activity of the combination therapy is superior to the antitumour activity to enzalutamide alone (enzalutamide + AZD5363 vs. enzalutamide + placebo).

Reporting group title	Phase II Randomised (Placebo)

Reporting group description:

A randomised, double blind phase II trial of enzalutamide in combination with AZD5363 versus enzalutamide alone will determine if the antitumour activity of the combination therapy is superior to the antitumour activity to enzalutamide alone (enzalutamide + AZD5363 vs. enzalutamide + placebo).

Subject analysis set title	Evaluable - randomised phase 2 - AZD5363
Subject analysis set type	Per protocol

Subject analysis set description:

Evaluable population for randomised phase 2 - experimental arm - evaluable for primary endpoint overall response

Subject analysis set title	Evaluable - randomised phase 2 - placebo
Subject analysis set type	Per protocol

Subject analysis set description:

Evaluable population for randomised phase 2 - placebo arm - evaluable for primary endpoint overall response

Subject analysis set title	Phase I - Dose level 1 - 320mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients allocated to dose elevel 1 of dose-fiding phase I

Subject analysis set title	Phase I - Dose level 2 - 480mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients allocated to dose elevel 2 of dose-fiding phase I

Subject analysis set title	Phase I - Dose level 1A - 400mg
Subject analysis set type	Safety analysis

Subject analysis set description:

Patients allocated to dose elevel 1A of dose-fiding phase I

Primary: Overall composite response

End point title	Overall composite response[1]

End point description:

The primary endpoint of response is defined on the basis of the following outcomes; if any of these occur without evidence of RECIST progression patients are considered to have responded:

- PSA decline of ≥50% confirmed by a second reading after 4 weeks
- Objective response (complete and/or partial response) by RECIST v1.1
- ONLY for patients with detectable circulating tumour cell counts ≥5/7.5ml blood at baseline,

conversion of CTC to <5/7.5ml blood nadir confirmed by a second reading after 4 weeks.
Only PSA and CTC assessments from week 12 onwards (to coincide with the first RECIST assessment) are considered to evaluate response, unless a PSA or CTC response are reached before cycle 4, and the response is maintained after 12 weeks of treatment and no evidence of radiological progression is seen at 12 weeks. This will also compute as a response in the primary endpoint.

End point type	Primary

End point timeframe:

While on combination treatment

Notes:

[1] - 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: Two cohorts forming part of the RE-AKT platform trial are single arm, non comparative. Therefore, we have not reported statistical analysis.

End point values	Phase I Safety run-in	Phase II Expansion	Evaluable - randomised phase 2 - AZD5363	Evaluable - randomised phase 2 - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	10	13	47	48
Units: responses	3	1	9	9

Statistical analyses

Statistical analysis title	Randomised phase 2 - primary endpoint
Comparison groups	Evaluable - randomised phase 2 - placebo v Evaluable - randomised phase 2 - AZD5363
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	0.4
Confidence interval	
level	90 %
sides	2-sided
lower limit	-12.8
upper limit	13.6

Primary: Dose-Limiting Toxicity - Phase I

End point title	Dose-Limiting Toxicity - Phase I[2]

End point description:

End point type	Primary

End point timeframe:

35-day DLT window

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: The RE-AKT phase I was a dose-finding study, with only descriptive statistics and rules to decide MDT were used; no statistical analysis was done.

End point values	Phase I - Dose level 1 - 320mg	Phase I - Dose level 2 - 480mg	Phase I - Dose level 1A - 400mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	4[3]	6[4]	
Units: Toxicities	0	2	1	

Notes:

[3] - 4 evaluable for DLT decisions

[4] - 6 evaluable for dose-escalating decisions

Statistical analyses

No statistical analyses for this end point

Secondary: Radiographic Progression-Free Survival (rPFS)

End point title	Radiographic Progression-Free Survival (rPFS)[5]

End point description:

Radiographic progression-free survival (rPFS) is defined by either RECIST progression and /or progression on bone scan. It is measured from the date of randomisation to the first occurrence of radiographic progression or death from any cause.

End point type	Secondary

End point timeframe:

rPFS is measured from the date of randomisation to the first occurrence of radiographic progression or death from any cause.

Notes:

[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: Two cohorts forming part of the RE-AKT platform trial are single arm, non comparative. Therefore, we have not reported statistical analysis.

End point values	Phase II Randomised (AZD5363)	Phase II Randomised (Placebo)	Evaluable - randomised phase 2 - AZD5363	Evaluable - randomised phase 2 - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	50	47	48
Units: Years				
median (inter-quartile range (Q1-Q3))	5.6 (2.8 to 11.0)	3.5 (2.7 to 8.4)	5.6 (2.8 to 11.0)	3.3 (2.7 to 8.4)

Statistical analyses

Statistical analysis title	Comparing treatment group - all patients
Comparison groups	Phase II Randomised (AZD5363) v Phase II Randomised (Placebo)

Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.3

Statistical analysis title	Comparing treatment group - evaluable patients
Comparison groups	Evaluable - randomised phase 2 - placebo v Evaluable - randomised phase 2 - AZD5363
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.44
upper limit	1.24

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[6]

End point description:

Progression-free survival (PFS) was measured from the date of trial entry until radiographic progression, unequivocal clinical progression or death. If no such event occurred while on observation, then PFS was censored at the last scheduled disease assessment on study.

End point type	Secondary

End point timeframe:

Progression-free survival (PFS) was measured from the date of trial entry until radiographic progression, unequivocal clinical progression or death.

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: Two cohorts forming part of the RE-AKT platform trial are single arm, non comparative. Therefore, we have not reported statistical analysis.

End point values	Phase II Randomised (AZD5363)	Phase II Randomised (Placebo)	Evaluable - randomised phase 2 - AZD5363	Evaluable - randomised phase 2 - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	50	47	48
Units: Years				
median (inter-quartile range (Q1-Q3))	5.3 (2.8 to 8.3)	2.9 (2.6 to 8.3)	5.3 (2.8 to 8.3)	2.9 (2.6 to 8.3)

Statistical analyses

Statistical analysis title	Comparing treatment group - all patients
Comparison groups	Phase II Randomised (AZD5363) v Phase II Randomised (Placebo)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.2

Statistical analysis title	Comparing treatment group - evaluable patients
Comparison groups	Evaluable - randomised phase 2 - AZD5363 v Evaluable - randomised phase 2 - placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.19

Secondary: Overall survival (OS)

End point title	Overall survival (OS)[7]

End point description:

End point type	Secondary

End point timeframe:

Overall survival is measured from the date of randomisation to the date of death (whatever the cause).

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: Two cohorts forming part of the RE-AKT platform trial are single arm, non comparative. Therefore, we have not reported statistical analysis.

End point values	Phase II Randomised (AZD5363)	Phase II Randomised (Placebo)	Evaluable - randomised phase 2 - AZD5363	Evaluable - randomised phase 2 - placebo
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	50	50	47	48
Units: Years				
median (inter-quartile range (Q1-Q3))	13.9 (6.3 to 20.5)	11.0 (5.6 to 19.7)	12.7 (6.4 to 20.0)	11.0 (5.6 to 19.7)

Statistical analyses

Statistical analysis title	Comparing treatment group - all patients
Comparison groups	Phase II Randomised (AZD5363) v Phase II Randomised (Placebo)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.15

Statistical analysis title	Comparing treatment group - evaluable patients
Comparison groups	Evaluable - randomised phase 2 - AZD5363 v Evaluable - randomised phase 2 - placebo
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.4

Secondary: Proportion of patients with at least 1 skeletal event

End point title	Proportion of patients with at least 1 skeletal event[8]

End point description:

End point type	Secondary

End point timeframe:

Skeletal-related events are defined as either the use of external beam radiotherapy to relieve skeletal symptoms or the occurrence of new symptomatic bone fractures (vertebral or non-vertebral) or the occurrence of spinal cord compression or a tumour rela

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: Two cohorts forming part of the RE-AKT platform trial are single arm, non comparative. Therefore, we have not reported statistical analysis.

End point values	Phase II Randomised (AZD5363)	Phase II Randomised (Placebo)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	50		
Units: Patients	6	14		

Statistical analyses

Statistical analysis title	Comparing treatment group - all patients
Comparison groups	Phase II Randomised (AZD5363) v Phase II Randomised (Placebo)
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After commencement of study treatment and within 30 days of last administration of study treatment.

Adverse event reporting additional description:

Non-serious adverse events reported are treatment emergent events. Treatment-emergent AEs are defined as any events that occur or worsen on or after first dose of study drug up through 30 days post last administration of study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Phase I Safety run-in

Reporting group description:

This population includes all enrolled patients who received at least 1 treatment dose of either of the treatment drugs.

Reporting group title	Phase II Expansion

Reporting group description:

This population includes all enrolled patients due to start combination treatment who received at least 1 dose of either of the treatment drugs in the combination.

Reporting group title	Phase II Randomised (AZD5363)

Reporting group description:

This population includes all enrolled patients who received at least 1 treatment of either of the treatment drugs.

Reporting group title	Phase II Randomised (Placebo)

Reporting group description:

This population includes all enrolled patients who received at least 1 treatment of either of the treatment drugs.

Serious adverse events	Phase I Safety run-in	Phase II Expansion	Phase II Randomised (AZD5363)
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 15 (60.00%)	7 / 13 (53.85%)	25 / 48 (52.08%)
number of deaths (all causes)	2	12	45
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	0 / 48 (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
Vasovagal collapse			

subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Blocked Catheter			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	3 / 48 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
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			
Angina pectoris			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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
Atrial fibrillation			

subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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			
Confusional state			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Spinal cord compression			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 13 (15.38%)	3 / 48 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinopathy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	0 / 48 (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 / 15 (0.00%)	1 / 13 (7.69%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	4 / 48 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
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 / 15 (0.00%)	1 / 13 (7.69%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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
Rash maculo-papular			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 15 (0.00%)	2 / 13 (15.38%)	4 / 48 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	3 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary retention			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	2 / 13 (15.38%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	4 / 48 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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 and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	3 / 48 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mobility decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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

Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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 pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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
Neck pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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
Bone pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impending femur fracture			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	0 / 48 (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
Infections and infestations			
Sepsis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			

subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	2 / 48 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	0 / 48 (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
Genitourinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes simplex			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	0 / 48 (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
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			

subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
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 / 15 (0.00%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Phase II Randomised (Placebo)		
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 50 (48.00%)		
number of deaths (all causes)	49		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vasovagal collapse			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Blocked Catheter			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine increased			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Confusional state			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhage intracranial			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinopathy			
subjects affected / exposed	0 / 50 (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	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 50 (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	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urosepsis				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Arthralgia				
subjects affected / exposed	2 / 50 (4.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Back pain				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mobility decreased				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Muscular weakness				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal pain				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neck pain				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone pain				

subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Femoral neck fracture				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Impending femur fracture				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Sepsis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infection				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cystitis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Encephalitis				

subjects affected / exposed	1 / 50 (2.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Genitourinary tract infection				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes simplex				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Acidosis				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	0 / 50 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyponatraemia				
subjects affected / exposed	0 / 50 (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	Phase I Safety run-in	Phase II Expansion	Phase II Randomised (AZD5363)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	13 / 13 (100.00%)	48 / 48 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 15 (0.00%)	2 / 13 (15.38%)	4 / 48 (8.33%)
occurrences (all)	0	2	4
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 15 (13.33%)	1 / 13 (7.69%)	4 / 48 (8.33%)
occurrences (all)	2	1	4
Fatigue			
subjects affected / exposed	6 / 15 (40.00%)	7 / 13 (53.85%)	29 / 48 (60.42%)
occurrences (all)	6	7	29
Oedema peripheral			
subjects affected / exposed	3 / 15 (20.00%)	1 / 13 (7.69%)	3 / 48 (6.25%)
occurrences (all)	3	1	3
Pyrexia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	3 / 48 (6.25%)
occurrences (all)	2	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 15 (6.67%)	1 / 13 (7.69%)	6 / 48 (12.50%)
occurrences (all)	1	1	6
Dyspnoea			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	7 / 48 (14.58%)
occurrences (all)	0	0	7
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 15 (13.33%)	1 / 13 (7.69%)	2 / 48 (4.17%)
occurrences (all)	2	1	2
Insomnia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	4 / 48 (8.33%)
occurrences (all)	2	0	4
Investigations			

Blood creatinine increased			
subjects affected / exposed	3 / 15 (20.00%)	2 / 13 (15.38%)	3 / 48 (6.25%)
occurrences (all)	3	2	3
Neutrophil count decreased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	4 / 48 (8.33%)
occurrences (all)	0	0	4
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 13 (7.69%)	3 / 48 (6.25%)
occurrences (all)	1	1	3
White blood cell count decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	3 / 48 (6.25%)
occurrences (all)	1	0	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	6 / 48 (12.50%)
occurrences (all)	0	0	6
Dysgeusia			
subjects affected / exposed	1 / 15 (6.67%)	2 / 13 (15.38%)	3 / 48 (6.25%)
occurrences (all)	1	2	3
Lethargy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	2 / 48 (4.17%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 15 (33.33%)	8 / 13 (61.54%)	19 / 48 (39.58%)
occurrences (all)	5	8	19
Abdominal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	7 / 48 (14.58%)
occurrences (all)	2	0	7
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	5 / 15 (33.33%)	3 / 13 (23.08%)	9 / 48 (18.75%)
occurrences (all)	5	3	9
Diarrhoea			
subjects affected / exposed	10 / 15 (66.67%)	11 / 13 (84.62%)	36 / 48 (75.00%)
occurrences (all)	10	11	36

Nausea			
subjects affected / exposed	7 / 15 (46.67%)	5 / 13 (38.46%)	20 / 48 (41.67%)
occurrences (all)	7	5	20
Vomiting			
subjects affected / exposed	4 / 15 (26.67%)	2 / 13 (15.38%)	19 / 48 (39.58%)
occurrences (all)	4	2	19
Dyspepsia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	1 / 48 (2.08%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	3 / 15 (20.00%)	1 / 13 (7.69%)	8 / 48 (16.67%)
occurrences (all)	3	1	8
Rash			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	10 / 48 (20.83%)
occurrences (all)	0	0	10
Pruritus			
subjects affected / exposed	0 / 15 (0.00%)	2 / 13 (15.38%)	4 / 48 (8.33%)
occurrences (all)	0	2	4
Dry skin			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	3 / 48 (6.25%)
occurrences (all)	0	1	3
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	6 / 48 (12.50%)
occurrences (all)	0	0	6
Haematuria			
subjects affected / exposed	2 / 15 (13.33%)	1 / 13 (7.69%)	5 / 48 (10.42%)
occurrences (all)	2	1	5
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	7 / 48 (14.58%)
occurrences (all)	2	0	7
Pain in extremity			
subjects affected / exposed	3 / 15 (20.00%)	3 / 13 (23.08%)	7 / 48 (14.58%)
occurrences (all)	3	3	7

Musculoskeletal chest pain			
subjects affected / exposed	2 / 15 (13.33%)	1 / 13 (7.69%)	6 / 48 (12.50%)
occurrences (all)	2	1	6
Bone pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 13 (15.38%)	3 / 48 (6.25%)
occurrences (all)	0	2	3
Muscular weakness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	5 / 48 (10.42%)
occurrences (all)	1	0	5
Arthralgia			
subjects affected / exposed	6 / 15 (40.00%)	3 / 13 (23.08%)	12 / 48 (25.00%)
occurrences (all)	6	3	12
Back pain			
subjects affected / exposed	4 / 15 (26.67%)	3 / 13 (23.08%)	13 / 48 (27.08%)
occurrences (all)	4	3	13
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	4 / 48 (8.33%)
occurrences (all)	1	0	4
Urinary tract infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	6 / 48 (12.50%)
occurrences (all)	0	0	6
Weight decreased			
subjects affected / exposed	3 / 15 (20.00%)	3 / 13 (23.08%)	5 / 48 (10.42%)
occurrences (all)	3	3	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 15 (53.33%)	4 / 13 (30.77%)	18 / 48 (37.50%)
occurrences (all)	8	4	18
Hyperglycaemia			
subjects affected / exposed	8 / 15 (53.33%)	1 / 13 (7.69%)	5 / 48 (10.42%)
occurrences (all)	8	1	5
Hypokalaemia			
subjects affected / exposed	4 / 15 (26.67%)	3 / 13 (23.08%)	7 / 48 (14.58%)
occurrences (all)	4	3	7
Hyponatraemia			

subjects affected / exposed	3 / 15 (20.00%)	0 / 13 (0.00%)	2 / 48 (4.17%)
occurrences (all)	3	0	2
Hypoalbuminaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 13 (0.00%)	3 / 48 (6.25%)
occurrences (all)	0	0	3

Non-serious adverse events	Phase II Randomised (Placebo)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	26 / 50 (52.00%)		
occurrences (all)	26		
Oedema peripheral			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Dyspnoea			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Neutrophil count decreased			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Dysgeusia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Lethargy			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	13		
Abdominal pain			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	13 / 50 (26.00%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	15		
Nausea			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	15		
Vomiting			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	8		
Dyspepsia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue			

disorders			
Musculoskeletal pain			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Pain in extremity			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	10		
Musculoskeletal chest pain			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Bone pain			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Muscular weakness			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Arthralgia			
subjects affected / exposed	11 / 50 (22.00%)		
occurrences (all)	11		
Back pain			
subjects affected / exposed	20 / 50 (40.00%)		
occurrences (all)	20		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	17 / 50 (34.00%)		
occurrences (all)	17		
Hyperglycaemia			

subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Hypokalaemia			
subjects affected / exposed	4 / 50 (8.00%)		
occurrences (all)	4		
Hyponatraemia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences (all)	2		
Hypoalbuminaemia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2015	Updates of adverse events in line with AZD5363 IB Edition 6. Remove reference to PCWG2, removed definition of progression from within the definition of response, as it is not needed. Change of phase I method to 3+3 instead of rolling six and clarification of wording to better reflect dose-escalation rule. Update to Phase I inclusion criteria. Clarification that the 9 PTEN patients must be fully evaluable for evaluation for the primary outcome in expansion cohort. Clarification of laboratory tests. Update to reflect switch from capsules of AZD5363 to tablets. Clarification to provide further details of the definition of evaluable population.
16 November 2016	Update to change the study design of the Expansion cohort within the protocol. Change to the eligibility criteria within the protocol. Addition of new sites/PI, removal of 1 site/PI. Update to Expansion cohort patient information sheet, consent for and GP letter. New patient documents for a sole Enzalutamide run-in phase within the Expansion cohort. e.g. patient diary card and patient card. Submission of AZD5363 Investigator Brochure Edition 7 for information.
12 February 2018	Updating the RSI and the protocol in line with AZD5363 IB Ed. 8 14/12/2016 and Enzalutamide SmPC dated 12/10/2017 undesirable effects.
24 May 2019	Updated to reflect change in formulation of AZD5363

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported