Clinical trial results:
The short term effects of an AKT inhibitor (AZD5363) on biomarkers of the AKT pathway and anti-tumour activity in a breast cancer paired biopsy study (STAKT Trial)

Summary

EudraCT number	2012-005019-14
Trial protocol	GB
Global end of trial date	30 July 2018

Results information

Result version number	v1 (current)
This version publication date	19 October 2018
First version publication date	19 October 2018

Trial information

Trial identification

Sponsor protocol code	12076

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02077569
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	University Park, nottingham, United Kingdom, NG7 2RD
Public contact	Professor J F R Robertson, University of Nottingham, +44 01332724881, John.robertson@nottingham.ac.uk
Scientific contact	Professor J F R Robertson, University of Nottingham, +44 01332724881, John.robertson@nottingham.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 November 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2017
Global end of trial reached?	Yes
Global end of trial date	30 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

PRIMARY OBJECTIVE
To compare the effect of three different dose levels of AZD5363 versus a placebo (dummy drug)on the reduction in the growth of cancer cells and the direct effect on selected biological markers of the AKT pathway of four and a half days treatment in oestrogen receptor positive breast cancers by measuring the biological changes in the tumour using the biomarkers outlined below:

- pPRAS40
- pGSK3b
- Ki67

Stage 1 will compare 480mg BD versus placebo.
Stage 2 will compare 360mg BD versus 240mg BD.
Secondary: 1) To assess the tolerability of four and a half days treatment of AZD5363. 2) To assess the effect of four and a half days treatment of a range of doses of AZD5363 on alternative biological markers which relate to anti-tumour activity of the AKT pathway

Protection of trial subjects:

patients were encouraged to report all side affects during their time on the study. Diaries were provided for patients to record dates and severity of any side affects experienced, emergency contact numbers were also included.

Background therapy:

none

Evidence for comparator:

none

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

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 48
Worldwide total number of subjects	48
EEA total number of subjects	48

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)	42
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Double blind randomised, placebo controlled, multicentre trial in terms of treatment allocation, performed in two stages, in females with breast cancer (Stage 2 will not be placebo controlled but will be double blind due to the different doses of AZD5363 being allocated).

Pre-assignment

Screening details:

Women, aged 18 years and over, able to give written informed consent.
No evidence of dementia, altered mental status or any psychiatric condition that would prohibit understanding, or rendering, of informed consent.
WHO performance status 0-1 with histological confirmation of ER positive invasive breast carcinoma Stage 1/2/3 or Stage 4 with pr

Period 1

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

Blinding implementation details:

Randomisation, treatment allocation, delivery of pre-packaged drug and enabling emergency unblinding via IWRS will be the responsibility of Fisher Clinical Services and Cenduit. The randomisation schemes will be produced by computer software which incorporates a standard procedure for generating random numbers. The patients will be allocated to treatment in balanced blocks. Medications will be allocated unique numerical identifiers.

Arms

Are arms mutually exclusive?	Yes
Arm title	Stage 1 IMP

Arm description:

480mg BD for 4.5 days

Arm type	Experimental
Investigational medicinal product name	AZD5363
Investigational medicinal product code	
Other name	AKT inhibitor
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

480mg BD capsule

Arm title	Stage 1 placebo

Arm description:

placebo given over 4.5 days

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

Dosage and administration details:

matched to IMP

Arm title	Stage 2 240mg IMP

Arm description: 240 mg BD for 4.5 days	
Arm type	Experimental
Investigational medicinal product name	AZD5363 240mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 240 mg for 4.5 days	
Arm title	Stage 2 360mg IMP
Arm description: 360mg IMP BD for 4.5 days	
Arm type	Experimental
Investigational medicinal product name	AZD5363 360mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 360mg IMP BD for 4.5 days	

Number of subjects in period 1	Stage 1 IMP	Stage 1 placebo	Stage 2 240mg IMP
Started	19	17	7
Completed	19	17	7

Number of subjects in period 1	Stage 2 360mg IMP
Started	5
Completed	5

Baseline characteristics

Reporting groups	
Reporting group title	Stage 1 IMP
Reporting group description:	
480mg BD for 4.5 days	
Reporting group title	Stage 1 placebo
Reporting group description:	
placebo given over 4.5 days	
Reporting group title	Stage 2 240mg IMP
Reporting group description:	
240 mg BD for 4.5 days	
Reporting group title	Stage 2 360mg IMP
Reporting group description:	
360mg IMP BD for 4.5 days	

Reporting group values	Stage 1 IMP	Stage 1 placebo	Stage 2 240mg IMP
Number of subjects	19	17	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	16	5
From 65-84 years	2	1	2
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	19	17	7

Reporting group values	Stage 2 360mg IMP	Total	
Number of subjects	5	48	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	4	42	
From 65-84 years	1	6	
85 years and over	0	0	

Gender categorical Units: Subjects			
Female	5	48	

Subject analysis sets	
Subject analysis set title	stage 1 IMP
Subject analysis set type	Full analysis
Subject analysis set description: All participants who completed IMP dosage of 4.5 days.	
Subject analysis set title	stage 1 placebo
Subject analysis set type	Full analysis
Subject analysis set description: all subjects who completed 4.5 days of placebo	
Subject analysis set title	Stage 2 240mg IMP
Subject analysis set type	Full analysis
Subject analysis set description: stage 2 240mg IMP	
Subject analysis set title	Stage 2 360mg IMP
Subject analysis set type	Full analysis
Subject analysis set description: Stage 2 360mg AZD5363	

Reporting group values	stage 1 IMP	stage 1 placebo	Stage 2 240mg IMP
Number of subjects	19	17	7
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	16	5
From 65-84 years	2	1	2
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	19	19	7

Reporting group values	Stage 2 360mg IMP		
Number of subjects	5		
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)	16		
From 65-84 years	1		
85 years and over	0		
Gender categorical Units: Subjects			
Female	5		

End points

End points reporting groups

Reporting group title	Stage 1 IMP
Reporting group description: 480mg BD for 4.5 days	
Reporting group title	Stage 1 placebo
Reporting group description: placebo given over 4.5 days	
Reporting group title	Stage 2 240mg IMP
Reporting group description: 240 mg BD for 4.5 days	
Reporting group title	Stage 2 360mg IMP
Reporting group description: 360mg IMP BD for 4.5 days	
Subject analysis set title	stage 1 IMP
Subject analysis set type	Full analysis
Subject analysis set description: All participants who completed IMP dosage of 4.5 days.	
Subject analysis set title	stage 1 placebo
Subject analysis set type	Full analysis
Subject analysis set description: all subjects who completed 4.5 days of placebo	
Subject analysis set title	Stage 2 240mg IMP
Subject analysis set type	Full analysis
Subject analysis set description: stage 2 240mg IMP	
Subject analysis set title	Stage 2 360mg IMP
Subject analysis set type	Full analysis
Subject analysis set description: Stage 2 360mg AZD5363	

Primary: Primary endpoints: changes in biomarkers

End point title	Primary endpoints: changes in biomarkers

End point description:

primary endpoint: pharmocodynamic biomarker analysis in tumour tissue, to assess the the biological effect of AZD5363 on markers of anti proliferation and the AKT pathway

- pPRAS40
- pGSK3b
- Ki67

End point type	Primary

End point timeframe:

analysis of tumour biomarker immediately following study biopsy compared to diagnostic biopsy.

End point values	stage 1 IMP	stage 1 placebo	Stage 2 240mg IMP	Stage 2 360mg IMP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	17	7	5
Units: Percentage change pre and post op tumour				
arithmetic mean (confidence interval 95%)				
pPRAS40	-43.68 (-56.71 to -30.65)	6.55 (-5.39 to 18.49)	350.65 (-587.61 to 1288.91)	-46.94 (-86.58 to -7.29)
pGSK3b	-41.63 (-57.46 to -25.80)	-0.87 (-22.08 to 20.33)	194.43 (-308.76 to 697.62)	-27.1 (-74.19 to 19.98)
Ki67	-38.3 (-57.56 to -19.08)	-12.1 (-36.00 to 11.78)	25.09 (-6.12 to 56.30)	-0.33 (-30.25 to 29.60)

Statistical analyses

Statistical analysis title	Stage 1 Primary o/c biomarker pPRAS40

Statistical analysis description:

Data analysis performed in SAS 9.3.
All data in the study summarized by group and time point and reported accordingly. Continuous data reported using mean (SD), while categorical data will be reported as N (%).

Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-50.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.89
upper limit	-31.73
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Primary o/c biomarker pGSK3b
Comparison groups	stage 1 placebo v stage 1 IMP
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0057
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (final values)
Point estimate	-41.63

Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.48
upper limit	-12.46
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 primary o/c biomarker Ki67
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0521
Method	Mixed models analysis
Parameter estimate	Median difference (final values)
Point estimate	-23.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-59.09
upper limit	0.29
Variability estimate	Standard error of the mean

Secondary: Secondary endpoints: changes in alternative biomarkers

End point title	Secondary endpoints: changes in alternative biomarkers

End point description:

To compare the anti-proliferative effect and the direct effect on selected markers of the AKT pathway of four and a half days treatment at three different dose levels of AZD5363 versus placebo in oestrogen receptor positive breast cancers by measuring the biological changes in the tumour and circulation via measurement of:
Tumour pAKT, caspase 3000, caspase 500, pS6, FOXO3a

End point type	Secondary

End point timeframe:

analysis of tumour biomarkers immediately following study biopsy compared to baseline/diagnostic biopsy

End point values	stage 1 IMP	stage 1 placebo	Stage 2 240mg IMP	Stage 2 360mg IMP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	17	7	5
Units: Percentage change pre and post op tumour				
arithmetic mean (confidence interval 95%)				

Tumour pAKT	107.01 (25.16 to 188.86)	5.91 (-24.94 to 36.77)	133.5 (21.79 to 245.21)	71.26 (-19.88 to 162.39)
Tumour pS6	-38.83 (-48.80 to 28.86)	-8.18 (-25.84 to 9.47)	-21.22 (-92.25 to 49.81)	-40.51 (-83.30 to 2.27)
Tumour FOX03a	12.01 (-13.52 to 37.55)	1.04 (-44.54 to 46.62)	79.04 (-17.18 to 275.27)	55.03 (-56.64 to 166.7)
Tumour caspase 3000	17.20 (-22.77 to 57.20)	5.33 (-36.35 to 47.01)	-42.83 (-78.61 to -7.05)	122.65 (-336.23 to 581.53)
Tumour caspase 500	64.74 (-45.42 to 174.95)	4.84 (-32.31 to 42.00)	-42.83 (-78.61 to -7.05)	122.65 (-336.23 to 581)

Statistical analyses

Statistical analysis title	Stage 1 secondary outcome tumour pAKT
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.011
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	116.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	29.3
upper limit	204.56
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 secondary outcome tumour pS6
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0031
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-29.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.84
upper limit	-11.12
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 secondary outcome tumour FOX03a
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3376
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	19.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.42
upper limit	60.22
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 secondary outcome tumour caspase 500
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.365
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	63.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-78
upper limit	204.61
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 secondary outcome caspase 3000
Comparison groups	stage 1 placebo v stage 1 IMP
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5702
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.076
upper limit	0.135

Variability estimate	Standard error of the mean

Other pre-specified: Exploratory endpoints: changes in biomarkers

End point title	Exploratory endpoints: changes in biomarkers

End point description:

Exploratory Endpoints:
Assessment of molecular aberrations of the AKT pathway and changes in blood and tissue based markers related to other cellular pathways
Platelet-rich plasma: pPRAS40, pGSK3b, P70S6K, pAKT, pAKT/AKT , PRP biomarker, PRP GSK-3b
Eyebrow hair: pPRAS40

End point type	Other pre-specified

End point timeframe:

Analysis of tumour biomarkers immediately following study biopsy compared to baseline/diagnostic biopsy

End point values	stage 1 IMP	stage 1 placebo	Stage 2 240mg IMP	Stage 2 360mg IMP
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17	11	7	5
Units: percentage				
arithmetic mean (confidence interval 95%)				
EH pPRAS 40	7.56 (-13.77 to 28.88)	23.56 (-30.86 to 77.98)	0 (0 to 0)	0 (0 to 0)
PRP Biomarker AKT	33.54 (-33.14 to 100.23)	206.58 (-288.46 to 701.61)	0 (0 to 0)	3.29 (-5.84 to 12.43)
PRP Biomarker GSK-3b	183.06 (-13.73 to 379.85)	502.13 (-695.51 to 1699.77)	31.19 (1.21 to 61.18)	7.61 (-27.20 to 42.42)
PRP Biomarker PRAS 40	87.85 (-67.43 to 243.05)	-10.38 (-34.54 to 13.78)	0 (0 to 0)	0 (0 to 0)
PRP Biomarker p70S6K	73.19 (-19.91 to 166.28)	983.53 (-1388.33 to 3355.39)	-2.01 (-37.74 to 33.73)	-10.56 (-27.47 to 6.35)
PRP Biomarker pAKT	-0.89 (-94.24 to 92.46)	155.18 (-33.28 to 343.63)	0 (0 to 0)	3.29 (-5.84 to 12.43)
PRP Biomarker pAKT/AKT	-40.04 (-63.75 to 16.33)	48.93 (-102.70 to 200.56)	0 (0 to 0)	0 (0 to 0)
PRP Biomarker pGSK 3b	17.98 (-144.09 to 180.05)	5.27 (-26.23 to 36.77)	-37.68 (-57.84 to -17.51)	-55.37 (-85.83 to -28.11)
PRP Biomarker pPRAS 40	-18.62 (-31.83 to 5.40)	7.18 (-11.18 to 25.55)	-4.37 (-14.14 to 5.40)	-7.85 (-20.65 to 4.95)
PRP Biomarker pp70S6K	-13.32 (-33.8 to 7.16)	14.56 (-11.68 to 40.79)	-4.66 (-25.31 to 34.63)	-6.13 (-25.57 to 13.32)

Statistical analyses

Statistical analysis title	Stage 1 Exploratory outcomes EH pPRAS40
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6608
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-9.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-55.83
upper limit	36.18
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratory outcomes PRP GSK-3b
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4184
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-327.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1169.56
upper limit	514.81
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratory outcomes PRP AKT
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3169
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-168.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-517.17
upper limit	180.88

Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratory outome PRP PRAS 40
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.157
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.43
upper limit	274.92
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratory outome PRP p70S6K
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2864
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-831.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2441.28
upper limit	777.8
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratory outcome PRP pAKT
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1653
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-111.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	-272.06
upper limit	50.45
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratpry outcome PRP pAKT/AKT
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1175
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-81.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-188.03
upper limit	25.01
Variability estimate	Standard error of the mean

Statistical analysis title	Staage 1 Exploratory outome PRP pGSK 3b
Comparison groups	stage 1 IMP v stage 1 placebo
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9848
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.492
Confidence interval	
level	95 %
sides	2-sided
lower limit	-160.14
upper limit	163.13
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratory outcome PRP pPRAS 40
Comparison groups	stage 1 IMP v stage 1 placebo

Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0153
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-27.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-48.51
upper limit	5.79
Variability estimate	Standard error of the mean

Statistical analysis title	Stage 1 Exploratory outome PRP pp70S6K
Comparison groups	stage 1 placebo v stage 1 IMP
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1146
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-20.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.72
upper limit	5.51
Variability estimate	Standard error of the mean

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events will be recorded and closely monitored until resolution, stabilisation, or until it has been shown that the study medication or treatment is not the cause.

Adverse event reporting additional description:

For the purpose of this trial, any detrimental change in a patient's condition, subsequent to their entering the trial and during the 30-day follow-up period after the last AZD5363/placebo capsule or tablet, should be considered an AE

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	4.0

Reporting groups

Reporting group title	stage 1 IMP
Reporting group description: AZD5363	
Reporting group title	stage 1 placebo
Reporting group description: 240mg/360mg AZD5363	
Reporting group title	Stage 2 240mg IMP
Reporting group description: STAGE 2 240mg AZD5363	
Reporting group title	Stage 2 360mg IMP
Reporting group description: Stage 2 360mg AZD5363	

Serious adverse events	stage 1 IMP	stage 1 placebo	Stage 2 240mg IMP
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)	3 / 17 (17.65%)	2 / 7 (28.57%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (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
Cardiac disorders			
Sinus tachycardia			

subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (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
General disorders and administration site conditions			
Migraine without aura			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (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
Dizziness			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (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
Neutropenic sepsis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (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
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacterial infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Stage 2 360mg IMP		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Delayed recovery from anaesthesia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Migraine without aura			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic sepsis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	stage 1 IMP	stage 1 placebo	Stage 2 240mg IMP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 19 (94.74%)	12 / 17 (70.59%)	7 / 7 (100.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
hypotension			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Phlebitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Abdominal pain and/or distension			
subjects affected / exposed	7 / 19 (36.84%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	7	1	0
Blood creatine increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Blood urea increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
chills			
subjects affected / exposed	3 / 19 (15.79%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Fatigue			
subjects affected / exposed	7 / 19 (36.84%)	3 / 17 (17.65%)	2 / 7 (28.57%)
occurrences (all)	7	3	2
impaired healing			

subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Injection site rash			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Malaise			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Paraesthesia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Puncture site swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 17 (11.76%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Vulval disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Early satiety			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Infusion site extravasation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
breast pain			

subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
cough			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Depression			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Irritability			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
restlessness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Investigations			
Ejection fraction decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Delayed recovery from anaesthesia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Post procedural haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

procedural pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Seroma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	2 / 7 (28.57%)
occurrences (all)	0	0	2
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
palpitations			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 19 (31.58%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	6	0	0
Dysgeusia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	10 / 19 (52.63%)	2 / 17 (11.76%)	1 / 7 (14.29%)
occurrences (all)	10	2	1
Hot flush			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Hyperaesthesia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Migraine			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Migraine without aura			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
neuralgia			

subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Parosmia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Blood bilirubin increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 17 (11.76%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Neutropenic sepsis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	2 / 7 (28.57%)
occurrences (all)	0	1	2
Face oedema			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
ear pain			

subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
External ear pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Mydriasis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Ocular hyperaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
blurred vision			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Eye pruritus			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Hordeolum			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	3 / 19 (15.79%)	3 / 17 (17.65%)	0 / 7 (0.00%)
occurrences (all)	3	3	0
Diarrhoea			
subjects affected / exposed	18 / 19 (94.74%)	4 / 17 (23.53%)	1 / 7 (14.29%)
occurrences (all)	25	4	1
dyspepsia			
subjects affected / exposed	4 / 19 (21.05%)	3 / 17 (17.65%)	2 / 7 (28.57%)
occurrences (all)	4	3	2
Faeces discoloured			

subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	3 / 19 (15.79%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	3	0	0
Mouth ulceration			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	10 / 19 (52.63%)	4 / 17 (23.53%)	3 / 7 (42.86%)
occurrences (all)	10	4	3
Oral pain			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
orophayangeal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	1 / 19 (5.26%)	3 / 17 (17.65%)	0 / 7 (0.00%)
occurrences (all)	1	3	0
Toothache			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
vomiting			
subjects affected / exposed	4 / 19 (21.05%)	1 / 17 (5.88%)	2 / 7 (28.57%)
occurrences (all)	4	1	2
Eructation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
alopecia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	1	1	0

Acne			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
rash			
subjects affected / exposed	5 / 19 (26.32%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Nocturia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Proteinuria			
subjects affected / exposed	5 / 19 (26.32%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	5	1	0
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Joint swelling			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			

subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Cystitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Febrile neutropenia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
post operative wound infection			
subjects affected / exposed	1 / 19 (5.26%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 17 (5.88%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
bacterial infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Hyperglycaemia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 17 (0.00%)	0 / 7 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Stage 2 360mg IMP		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
hypotension			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Phlebitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Abdominal pain and/or distension			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood creatine increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Blood urea increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Chest pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
chills			

subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Fatigue				
subjects affected / exposed	5 / 5 (100.00%)			
occurrences (all)	7			
impaired healing				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Injection site rash				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Malaise				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Oedema peripheral				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Paraesthesia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Puncture site swelling				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Pyrexia				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Vulval disorder				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Early satiety				
subjects affected / exposed	0 / 5 (0.00%)			
occurrences (all)	0			
Infusion site extravasation				
subjects affected / exposed	1 / 5 (20.00%)			
occurrences (all)	1			
Insomnia				

subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Reproductive system and breast disorders			
breast pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Vulvovaginal pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
cough			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Depression			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
restlessness			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Investigations			
Ejection fraction decreased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			

Delayed recovery from anaesthesia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Post procedural haemorrhage subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
procedural pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Seroma subjects affected / exposed occurrences (all)	2 / 5 (40.00%) 2		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
palpitations subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	5 / 5 (100.00%) 5		
Hot flush subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1		
Hyperaesthesia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0		
Migraine			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Migraine without aura			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
neuralgia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Tremor			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Parosmia			
subjects affected / exposed	3 / 5 (60.00%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Neutropenia			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Neutropenic sepsis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		

Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
ear pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
External ear pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Eye disorders			
Mydriasis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Ocular hyperaemia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
blurred vision			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Eye pruritus			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Hordeolum			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
Campylobacter gastroenteritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Constipation			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
dyspepsia			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Faeces discoloured			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Glossodynia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	5 / 5 (100.00%)		
occurrences (all)	5		
Oral pain			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
orophayangeal pain			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Toothache			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
vomiting			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Eructation			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			

alopecia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Acne			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Dermatitis acneiform			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pruritus			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
rash			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Nocturia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Proteinuria			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	2 / 5 (40.00%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Myalgia			

subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Osteoarthritis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
post operative wound infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Urinary tract infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)		
occurrences (all)	0		
bacterial infection			
subjects affected / exposed	1 / 5 (20.00%)		
occurrences (all)	1		

Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all)	 0 / 5 (0.00%) 0 2 / 5 (40.00%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2013	patient pathway clarifications and typographical errors corrected.SA/01/13 documents changed: protocol V2.0 participant consent form v3.0 participant information sheet v3.0 GP letter v2.0 patient information and diary: stage1 day 1-5 v1.0 patient information and diary: stage2 day 1-5 v1.0 patient information and diary: day 5-34 v1.0
16 January 2014	SA/02/14 Appendix 12: change to concomitant medications re antidepressants and statins (reverted to advisory) Appendix 13 added, typographical error corrected, updated information re sites and dates, anaesthetic advisory added, poster added. GP letter amended to provide Appendix 12 and 13 updated information. Protocol v3.0 11/01/14 poster v1 added GP letter 2.1
17 April 2014	Trial/study personnel and contact details updated: Edinburgh PI details changed: Coventry removed as a participating site. protocol v 4.0
11 July 2014	change to eligibility criteria to include pre-menopausal women; Increase in the number of participating sites; Reduction in minimum age to 18 years; Addition of pregnancy testing and contraception requirements for pre-menopausal women; mandatory 8 hr PK/PRP samples replaced with optional 6hr samples; removal of exclusion criterion 2 regarding HRT; addition of new information in Appendix 12 as supplied by AZ. Protocol v 5.0 consent pre-menopausal v1.0 consent post-menopausa v4.0 participant information sheet pre-menopausal v4.0 patient letter v1.0 summary information leaflet v1.0 GP letter v3.0

14 September 2015	Change of AZD5363 formulation from capsules to tablets;addition of information on new causally associated AZ of hypersensitivity and update to details on other causally assosciated AEs; addition of detail around visit 3 pre-dose blood glucose serum samples; inclusion of patient ID and name of participant on all pages of consent forms and patient information and diary booklets; clarification that tumour total AKT and PTEN are exploratory endpoints; new eligibility criteria allowing patients with new primary breast tumours despite prior endocrine treatment for an earlier breast tumour to considered eligible: definition of what constitutes an evaluable patient included; clarification around numbers of patients require in both stages. protocol V6.0 participant information sheet pre-menopausal V2.0 patient information sheet post-menopausal V5.0 consent pre-menopausal V1.1 consent post-menopausal V4.1 GP letter V4.0 patient info and diary stage 1 day 1-5 V2.0 patient info and diary stage 2 day 1-5 V2.0 patient info and diary day 5-34 V2.0 summary information leaflet V2.0 investigator brochure edition 6
02 December 2015	Removal of placebo arm in stage 2; Removal of eyebrow hair sampling in stage2; Removal of Tayside and Lincolnshire sites. Protocol V7.0 30/10/15 Participant information sheet pre-menopausal V3 30-10-15 Consent form post-menopausal V6 30-10-2015 consent form pre-menopausal V2 30-10-2015 consent form post menopausal V5 30-10-15 GP letter V5 30-10-15 summary information leaflet V3.3 30-10-15
21 July 2016	DMC,TSC, trial statistician, the funder and CI request and support the substantial amendment 08. This amendment requires to un-blind stage 1 for scientific not safety reasons. in addition to the substantial amendment the following minor amendments were submitted. clarification of trial staff since the last amendment these changes are in management staff only. Clarification that signed ICF will be filed in site File during the study p70. clarification of monitoring scheduling as per monitoring plan p73 clarification of IMP supply appendix 1- study drug manufacture. addition of text: note for stage2 placebo will not be manufactured, shipped or dispensed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

There were no pre-planned analyses as Phase 1 & 2 were separate, sequential phases and therefore non-randomised comparisons. In addition the number of patients per group in Phase 2 were only half that of the groups in Phase 1. The data are presented

Notes: