



Clinical trial results:

A Phase I/II, Multicentre, Study Comprising a Safety Run-In of AZD5363 when Combined with Paclitaxel in Patients with Advanced or Metastatic Breast Cancer; Followed by a Randomised Expansion of AZD5363 when Combined with Paclitaxel vs. Paclitaxel plus Placebo in Patients with ER-Positive Advanced or Metastatic Breast Cancer, Stratified by PIK3CA Mutation Status (BEECH).

Summary

EudraCT number	2011-006312-31
Trial protocol	GB CZ
Global end of trial date	03 October 2022

Results information

Result version number	v1
This version publication date	08 January 2023
First version publication date	08 January 2023

Trial information

Trial identification

Sponsor protocol code	D360C00002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01625286
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Forskargatan, Sodertalje, Sweden, SE-151 85
Public contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, +1 877-240-9479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2016
Global end of trial reached?	Yes
Global end of trial date	03 October 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part A: To assess the safety and tolerability of AZD5363 when combined with weekly paclitaxel in patients with advanced or metastatic breast cancer, and to recommend, by assessment of dose-limiting toxicities (DLTs) and other safety, tolerability, PK, and PDc data, a dose and schedule of AZD5363 for further study when combined with weekly paclitaxel.

Part B: To assess the relative efficacy of AZD5363 when combined with weekly paclitaxel compared with weekly paclitaxel plus placebo by assessment of PFS in the overall advanced or metastatic ER-positive breast cancer population

Protection of trial subjects:

After each dose level during Part A of the study, the SRC evaluated the safety and tolerability and pharmacokinetics of AZD5363 to decide the next dose.

During the Part B Randomised Phase of the study, an independent SRC (ISRC) monitored safety and tolerability in the study by means of reviews of safety data at approximately 3 to 6 monthly intervals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 October 2012
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: 29
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Mexico: 15
Country: Number of subjects enrolled	Peru: 26
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Singapore: 4
Worldwide total number of subjects	148
EEA total number of subjects	46

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)	115
From 65 to 84 years	33
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Part A: Patients were recruited at 9 study centres in 3 countries; 44 patients were enrolled in this part of the study.

Part B: Patients were recruited in 40 study centres in 11 countries; 194 patients were enrolled in this part of the study, of which 51 patients had a tumour detectable as carrying a PIK3CA mutation.

Pre-assignment

Screening details:

Female patients aged ≥ 18 years, with histological or cytological confirmation of ER-positive and HER2-negative breast cancer, with evidence of relapsed advanced or metastatic disease.

Period 1

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

Blinding implementation details:

Part A was an open-label phase, Part B double-blind

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A Schedule 1 560 mg bd

Arm description:

Schedule 1 - AZD5363 560 mg bd (2 days on/5 days off) with Paclitaxel 90 mg/m² once weekly. 3/4 weeks.

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

Dosage and administration details:

An intermittent dosing schedule of 560 mg bd (1120 mg daily)

Arm title	Part A Schedule 1 640 mg bd
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Arm description:

Schedule 1 - AZD5363 640 mg bd (2 days on/5 days off) with Paclitaxel 90 mg/m² once weekly. 3/4 weeks.

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

Dosage and administration details:

An intermittent dosing schedule of 640 mg bd

Arm title	Part A Schedule 2 360 mg bd
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Arm description:

Schedule 2 - AZD5363 360 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m² once weekly. 3/4

weeks.

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

Dosage and administration details:

An intermittent dosing schedule of 360 mg bd

Arm title	Part A Schedule 2 400 mg bd
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Arm description:

Schedule 2 - AZD5363 400 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m² once weekly. 3/4 weeks.

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

Dosage and administration details:

An intermittent dosing schedule of 400 mg bd

Arm title	Part A Schedule 2 480 mg bd
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Arm description:

Schedule 2 - AZD5363 480 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m² once weekly. 3/4 weeks.

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

Dosage and administration details:

An intermittent dosing schedule of 480 mg bd

Arm title	Part B AZD5363
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Arm description:

(4 days on/3 days off) with Paclitaxel 90 mg/m² once weekly

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

Dosage and administration details:

An intermittent dosing schedule of 400 mg bd (4 days on / 3 days off) administered in combination with paclitaxel

Arm title	Part B Placebo
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Arm description:

(4 days on/3 days off) with Paclitaxel 90 mg/m² once weekly

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

Dosage and administration details:

An intermittent dosing schedule of 400 mg bd (4 days on / 3 days off) placebo administered in combination with paclitaxel

Number of subjects in period 1	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd
Started	12	8	5
Received AZD5363/Placebo treatment	12	8	5
Did not receive AZD5363/Placebo trt	0 ^[1]	0 ^[2]	0
Completed	6	4	0
Not completed	6	4	5
Adverse event, serious fatal	-	-	1
Consent withdrawn by subject	-	1	-
Adverse event, non-fatal	-	-	-
Any reason not specifically recorded	-	-	-
Progressive disease	6	3	4
Lost to follow-up	-	-	-

Number of subjects in period 1	Part A Schedule 2 400 mg bd	Part A Schedule 2 480 mg bd	Part B AZD5363
Started	7	6	54
Received AZD5363/Placebo treatment	7	6	54
Did not receive AZD5363/Placebo trt	0	0	0 ^[3]
Completed	0	0	40
Not completed	7	6	14
Adverse event, serious fatal	1	-	11
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	-	1	2
Any reason not specifically recorded	-	-	1
Progressive disease	5	5	-
Lost to follow-up	-	-	-

Number of subjects in period 1	Part B Placebo
Started	56
Received AZD5363/Placebo treatment	55
Did not receive AZD5363/Placebo trt	1 ^[4]
Completed	37
Not completed	19

Adverse event, serious fatal	16
Consent withdrawn by subject	1
Adverse event, non-fatal	1
Any reason not specifically recorded	-
Progressive disease	-
Lost to follow-up	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed minus those that left.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected the number of subjects will be greater than, or equal to the number that completed minus those that left.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected the number of subjects will be greater than, or equal to the number that completed minus those that left.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected the number of subjects will be greater than, or equal to the number that completed minus those that left.

Baseline characteristics

Reporting groups

Reporting group title	Part A Schedule 1 560 mg bd
Reporting group description: Schedule 1 - AZD5363 560 mg bd (2 days on/5 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 1 640 mg bd
Reporting group description: Schedule 1 - AZD5363 640 mg bd (2 days on/5 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 2 360 mg bd
Reporting group description: Schedule 2 - AZD5363 360 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 2 400 mg bd
Reporting group description: Schedule 2 - AZD5363 400 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 2 480 mg bd
Reporting group description: Schedule 2 - AZD5363 480 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.	
Reporting group title	Part B AZD5363
Reporting group description: (4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly	
Reporting group title	Part B Placebo
Reporting group description: (4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly	

Reporting group values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd
Number of subjects	12	8	5
Age, Customized Units: Subjects			
<50	5	3	1
>=50 - <65	5	2	3
>=65	2	3	1
Age Continuous Units: Years			
arithmetic mean	52.2	58.8	56.6
standard deviation	± 9.92	± 12.78	± 10.26
Sex: Female, Male Units: Subjects			
Female	12	8	5
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	1	0	0
Black Or African American	1	0	0
White	10	8	5

American Indian or Alaska Native	0	0	0
Other	0	0	0

Reporting group values	Part A Schedule 2 400 mg bd	Part A Schedule 2 480 mg bd	Part B AZD5363
Number of subjects	7	6	54
Age, Customized Units: Subjects			
<50	4	2	19
>=50 - <65	3	3	23
>=65	0	1	12
Age Continuous Units: Years arithmetic mean standard deviation	47.1 ± 9.41	49.8 ± 13.12	54.3 ± 10.01
Sex: Female, Male Units: Subjects			
Female	7	6	54
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Asian	0	0	12
Black Or African American	0	0	0
White	7	6	24
American Indian or Alaska Native	0	0	15
Other	0	0	3

Reporting group values	Part B Placebo	Total	
Number of subjects	56	148	
Age, Customized Units: Subjects			
<50	16	50	
>=50 - <65	26	65	
>=65	14	33	
Age Continuous Units: Years arithmetic mean standard deviation	57.4 ± 11.38	-	
Sex: Female, Male Units: Subjects			
Female	56	148	
Male	0	0	
Race/Ethnicity, Customized Units: Subjects			
Asian	15	28	
Black Or African American	0	1	
White	18	78	
American Indian or Alaska Native	16	31	
Other	7	10	

End points

End points reporting groups

Reporting group title	Part A Schedule 1 560 mg bd
Reporting group description: Schedule 1 - AZD5363 560 mg bd (2 days on/5 days off) with Paclitaxel 90 mg/m ² once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 1 640 mg bd
Reporting group description: Schedule 1 - AZD5363 640 mg bd (2 days on/5 days off) with Paclitaxel 90 mg/m ² once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 2 360 mg bd
Reporting group description: Schedule 2 - AZD5363 360 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m ² once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 2 400 mg bd
Reporting group description: Schedule 2 - AZD5363 400 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m ² once weekly. 3/4 weeks.	
Reporting group title	Part A Schedule 2 480 mg bd
Reporting group description: Schedule 2 - AZD5363 480 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m ² once weekly. 3/4 weeks.	
Reporting group title	Part B AZD5363
Reporting group description: (4 days on/3 days off) with Paclitaxel 90 mg/m ² once weekly	
Reporting group title	Part B Placebo
Reporting group description: (4 days on/3 days off) with Paclitaxel 90 mg/m ² once weekly	

Primary: Dose-limiting toxicity (DLT) Events - Part A

End point title	Dose-limiting toxicity (DLT) Events - Part A ^[1]
End point description: An Adverse Event (AE) or laboratory abnormality considered to be related to study drug, that starts at any time during the DLT evaluation period (Cycle 1) and is dose limiting	
End point type	Primary
End point timeframe: During Part A DLT evaluation period (Cycle 1, up to 28 days)	
Notes:	

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was performed. This was the safety run-in part of the study, where the primary purpose was to assess DLTs rather than to compare treatment groups, so no comparative analyses were conducted.

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	6	5	7
Units: participants	0	2	0	0

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	0 ^[2]	0 ^[3]	
Units: participants	2			

Notes:

[2] - DLTs were not assessed in Part B (the randomized part of the study)

[3] - DLTs were not assessed in Part B (the randomized part of the study)

Statistical analyses

No statistical analyses for this end point

Primary: Progression Free Survival (PFS) - Part B

End point title	Progression Free Survival (PFS) - Part B
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End point description:

Time from randomisation to date of objective disease progression or death (by any cause in the absence of progression). Progression defined using Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1), as a $\geq 20\%$ increase in the sum of diameters of target lesions, taking as reference the smallest sum on the study, and an absolute increase of $\geq 5\text{mm}$, or progression of non-target lesions or the appearance of new lesions.

End point type	Primary
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End point timeframe:

From randomisation date to date of objective disease progression or death (by any cause) whichever came first, assessed every 12 wks (median total treatment duration AZD5363=325.5 days; Placebo=245 days)

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[4]	0 ^[5]	0 ^[6]	0 ^[7]
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[4] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[5] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[6] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[7] - The endpoint was not assessed in Part A (the safety run-in part of the study)

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[8]	54	56	
Units: Months				
median (confidence interval 95%)	(to)	10.9 (8.3 to 12.4)	8.4 (8.2 to 10.8)	

Notes:

[8] - The endpoint was not assessed in Part A (the safety run-in part of the study)

Statistical analyses

Statistical analysis title	PFS - Part B
Comparison groups	Part B Placebo v Part B AZD5363
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.308 ^[10]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.8
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.6
upper limit	1.06

Notes:

[9] - A hazard ratio < 1 favours AZD5363

[10] - 2-sided p-value

Secondary: Change in tumour size at 12 weeks

End point title	Change in tumour size at 12 weeks
End point description:	
Percentage change from baseline to week 12 in sum of longest diameters of target lesions as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1). Based on patients with measurable disease who had sufficient data available to either calculate or impute a change at 12 weeks	
End point type	Secondary
End point timeframe:	
RECIST tumour assessments every 12 weeks	

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	7	5	5
Units: % change from baseline				
arithmetic mean (standard deviation)	-11.0 (± 33.42)	-15.7 (± 13.33)	-19.1 (± 17.73)	-18.3 (± 37.74)

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
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Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	53	55	
Units: % change from baseline				
arithmetic mean (standard deviation)	-10.2 (± 24.84)	-34.2 (± 28.91)	-25.4 (± 35.87)	

Statistical analyses

Statistical analysis title	Percentage change in tumour size at Week 12
Comparison groups	Part B AZD5363 v Part B Placebo
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.081 ^[11]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-8.9
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-17.1
upper limit	-0.8

Notes:

[11] - 1-sided p-value

Secondary: Objective Response Rate (ORR) at week 12

End point title	Objective Response Rate (ORR) at week 12
End point description:	Number of patients who have at least one visit response of Complete Response or Partial Response prior to any evidence of progression at week 12 as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) for target lesions (TL) and assessed by MRI or CT: Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Complete Response (CR), disappearance of all target lesions, any pathological lymph nodes selected as TLs must have a reduction in short axis to $< 10\text{mm}$; Objective Response Rate (ORR) = CR + PR
End point type	Secondary
End point timeframe:	RECIST tumour assessments every 12 weeks

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	5	7
Units: Number of participants	5	1	0	0

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	54	56	
Units: Number of participants	0	27	24	

Statistical analyses

No statistical analyses for this end point

Secondary: Best Objective Response (BOR)

End point title	Best Objective Response (BOR)
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End point description:

Number of patients, taking their BOR, which is their best objective tumour response based on RECIST measurements throughout the whole study as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) for target lesions (TL) and assessed by MRI or CT: Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Complete Response (CR), disappearance of all target lesions, any pathological lymph nodes selected as TLs must have a reduction in short axis to $< 10\text{mm}$.

End point type	Secondary
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End point timeframe:

From date of randomisation, assessed every 12 weeks (median total treatment duration AZD5363 = 325.5 days; Placebo = 245 days).

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	5	7
Units: Participants				
Complete Response (CR)	0	0	0	0
Partial Response (PR)	0	2	1	1
Stable Disease (SD)	7	4	3	4
Progression	4	1	1	1
Not Evaluable (NE)	1	1	0	1

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	54	56	
Units: Participants				
Complete Response (CR)	0	3	4	
Partial Response (PR)	0	29	28	
Stable Disease (SD)	3	14	14	
Progression	2	6	8	

Not Evaluable (NE)	1	2	2	
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Statistical analyses

No statistical analyses for this end point

Secondary: Overall Objective Response Rate

End point title	Overall Objective Response Rate
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End point description:

Number of patients, taking their best objective tumour response based on RECIST measurements throughout the whole study as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) for target lesions (TL) and assessed by MRI or CT: Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Complete Response (CR), disappearance of all target lesions, any pathological lymph nodes selected as TLs must have a reduction in short axis to $< 10\text{mm}$. Overall Response Rate (ORR) = CR + PR

End point type	Secondary
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End point timeframe:

From date of randomisation, assessed every 12 weeks (median total treatment duration AZD5363 = 325.5 days; Placebo = 245 days).

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	5	7
Units: Number of participants	0	2	1	1

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	54	56	
Units: Number of participants	0	32	32	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects Without Progressive Disease at Week 12 - Part A

End point title	Number of subjects Without Progressive Disease at Week 12 - Part A
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End point description:

Number of patients with a 12 week visit response of CR, PR or SD (as defined by RECIST 1.1) with no evidence of previous progression as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) for target lesions (TL) and assessed by MRI or CT: Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Complete Response (CR), disappearance of all target lesions, any pathological lymph nodes selected as TLs must have a reduction in short axis to $<10\text{mm}$.

End point type	Secondary
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End point timeframe:

up to 12 weeks

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	12	8	5	7
Units: Participants	6	5	3	4

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	6	0 ^[12]	0 ^[13]	
Units: Participants	2			

Notes:

[12] - The endpoint was not assessed in Part B (the randomized part of the study)

[13] - The endpoint was not assessed in Part B (the randomized part of the study)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) - Part B

End point title	Duration of Response (DOR) - Part B
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End point description:

Date of first documentation of response (Complete Response/Partial Response) until the date of disease progression as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) for target lesions (TL) and assessed by MRI or CT: Partial Response (PR), $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; Complete Response (CR), disappearance of all target lesions, any pathological lymph nodes selected as TLs must have a reduction in short axis to $<10\text{mm}$. If a subject does not progress following a response, then their DOR will use the PFS censoring time.

End point type	Secondary
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End point timeframe:

From date of randomisation, assessed every 12 weeks (median total treatment duration AZD5363 = 325.5 days; Placebo = 245 days).

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[14]	0 ^[15]	0 ^[16]	0 ^[17]
Units: Months				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[14] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[15] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[16] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[17] - The endpoint was not assessed in Part A (the safety run-in part of the study)

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[18]	54	56	
Units: Months				
median (confidence interval 95%)	(to)	8.3 (6 to 11.3)	8.2 (5.6 to 10.6)	

Notes:

[18] - The endpoint was not assessed in Part A (the safety run-in part of the study)

Statistical analyses

No statistical analyses for this end point

Secondary: Durable Response Rate (DRR) - Part B

End point title	Durable Response Rate (DRR) - Part B
End point description:	
Number of patients who have a Complete Response (CR) or Partial Response (PR) lasting continuously for at least 24 weeks as defined by Response Evaluation Criteria In Solid Tumours (RECIST version 1.1) for target lesions (TL) and assessed by MRI or CT: PR, $\geq 30\%$ decrease in the sum of the longest diameter of target lesions; CR, disappearance of all target lesions, any pathological lymph nodes selected as TLs must have a reduction in short axis to $<10\text{mm}$.	
End point type	Secondary
End point timeframe:	
From date of randomisation, assessed every 12 weeks (median total treatment duration AZD5363 = 325.5 days; Placebo = 245 days).	

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[19]	0 ^[20]	0 ^[21]	0 ^[22]
Units: Number of participants				

Notes:

[19] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[20] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[21] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[22] - The endpoint was not assessed in Part A (the safety run-in part of the study)

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[23]	54	56	
Units: Number of participants		26	21	

Notes:

[23] - The endpoint was not assessed in Part A (the safety run-in part of the study)

Statistical analyses

Statistical analysis title	Durable response rate (Part B)
Comparison groups	Part B AZD5363 v Part B Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.139 ^[24]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.53
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.93
upper limit	2.54

Notes:

[24] - 1-sided p-value

Secondary: Overall Survival - Part B

End point title	Overall Survival - Part B
End point description:	The interval between the date of randomisation and the date of patient death due to any cause. All Part B patients were analysed, number of deaths is presented.
End point type	Secondary
End point timeframe:	From date of randomisation, assessed every 12 weeks, up until the time of final statistical analysis. (median total treatment duration AZD5363 = 325.5 days; Placebo = 245 days).

End point values	Part A Schedule 1 560 mg bd	Part A Schedule 1 640 mg bd	Part A Schedule 2 360 mg bd	Part A Schedule 2 400 mg bd
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0 ^[25]	0 ^[26]	0 ^[27]	0 ^[28]
Units: months				
median (confidence interval 95%)	(to)	(to)	(to)	(to)

Notes:

[25] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[26] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[27] - The endpoint was not assessed in Part A (the safety run-in part of the study)

[28] - The endpoint was not assessed in Part A (the safety run-in part of the study)

End point values	Part A Schedule 2 480 mg bd	Part B AZD5363	Part B Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0 ^[29]	54	56	
Units: months				
median (confidence interval 95%)	(to)	32.8 (21.3 to 32.8)	999 (20.9 to 999)	

Notes:

[29] - The endpoint was not assessed in Part A (the safety run-in part of the study)

Statistical analyses

Statistical analysis title	Analysis of overall survival (Part B)
Comparison groups	Part B AZD5363 v Part B Placebo
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.482 ^[30]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.48
upper limit	1.24

Notes:

[30] - 2-sided p-value

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time of signature of informed consent throughout the treatment period up to and including the follow-up period (median follow-up AZD5363 16.9 months; Placebo 15.2 months)

Adverse event reporting additional description:

The 5% threshold is applied to trt schedule in Part A. Part A AEs were coded with MedDRA v20.0 (schedule 1) or v18.1 (schedule 2). The 5% threshold is applied to each Part B trt arm and Part B AEs were coded with MedDRA v19.1.

1 patient in the placebo arm did not receive placebo trt (hence n=56 for All Cause Mortality, n=55 for SAEs/AEs)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	1819.120

Reporting groups

Reporting group title	Part A Schedule 1 560 mg bd
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Reporting group description:

Schedule 1 - AZD5363 560 mg bd (2 days on/5 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.

Reporting group title	Sched 1 - AZD5363 640 mg bd
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Reporting group description:

(2 days on/5 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.

Reporting group title	Sched 2 - AZD5363 360 mg bd
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Reporting group description:

(4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.

Reporting group title	Sched 2 - AZD5363 400 mg bd
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Reporting group description:

(4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.

Reporting group title	Part A Schedule 2 480 mg bd
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Reporting group description:

Schedule 2 - AZD5363 480 mg bd (4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly. 3/4 weeks.

Reporting group title	Part B AZD5363
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Reporting group description:

(4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly

Reporting group title	Part B Placebo
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Reporting group description:

(4 days on/3 days off) with Paclitaxel 90 mg/m2 once weekly

Serious adverse events	Part A Schedule 1 560 mg bd	Sched 1 - AZD5363 640 mg bd	Sched 2 - AZD5363 360 mg bd
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 12 (25.00%)	3 / 8 (37.50%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Salivary gland cancer			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (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
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Pleural effusion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Pulmonary embolism			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Stridor			

subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Upper limb fracture			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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			
Anaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (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
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (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
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Ascites			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Periodontal disease			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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 pruritic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (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
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Catheter site cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Device related infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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

Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Pyelonephritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Urinary tract infection bacterial			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (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
Urosepsis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Hyperglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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
Hyponatraemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (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

Serious adverse events	Sched 2 - AZD5363 400 mg bd	Part A Schedule 2 480 mg bd	Part B AZD5363
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	4 / 6 (66.67%)	13 / 54 (24.07%)
number of deaths (all causes)	1	0	13
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Salivary gland cancer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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			
Pyrexia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Pleural effusion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Pulmonary embolism			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Stridor			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (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
Febrile neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (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			
Diarrhoea			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Periodontal disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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 pruritic			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (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
Acute kidney injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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			
Back pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (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
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (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
Catheter site cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Device related infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 54 (7.41%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Pyelonephritis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Urosepsis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
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	Part B Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 55 (14.55%)		
number of deaths (all causes)	15		
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Salivary gland cancer			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Stridor			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lethargy			
subjects affected / exposed	0 / 55 (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	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Periodontal disease			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Rash pruritic			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 55 (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 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Catheter site cellulitis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pneumonia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyelonephritis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection bacterial			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 55 (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	Part A Schedule 1 560 mg bd	Sched 1 - AZD5363 640 mg bd	Sched 2 - AZD5363 360 mg bd
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	8 / 8 (100.00%)	5 / 5 (100.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Hypertension			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Hot flush			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Lymphoedema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 12 (50.00%)	5 / 8 (62.50%)	1 / 5 (20.00%)
occurrences (all)	12	22	4
Device breakage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	2 / 5 (40.00%)
occurrences (all)	2	0	4
Oedema peripheral			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Peripheral swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Pyrexia			

subjects affected / exposed	1 / 12 (8.33%)	3 / 8 (37.50%)	2 / 5 (40.00%)
occurrences (all)	1	3	2
Influenza like illness			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Suprapubic pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Catheter site related reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Face oedema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hyperthermia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Breast discharge			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Pelvic pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Vaginal discharge			

subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Menorrhagia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 12 (41.67%)	3 / 8 (37.50%)	1 / 5 (20.00%)
occurrences (all)	6	4	1
Productive cough			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	2 / 5 (40.00%)
occurrences (all)	0	0	2
Dysphonia			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	2	0	1
Dyspnoea exertional			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	2 / 12 (16.67%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Epistaxis			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Nasal dryness			
subjects affected / exposed	2 / 12 (16.67%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Nasal obstruction			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			

subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 4	3 / 8 (37.50%) 4	1 / 5 (20.00%) 1
Rhinitis allergic subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0
Psychiatric disorders			
Depressed mood subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	1 / 5 (20.00%) 1
Insomnia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 3	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	1 / 8 (12.50%) 2	0 / 5 (0.00%) 0
Sleep disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0
Confusional state subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0
Depression subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Hallucination subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0
Irritability subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0
Investigations			
Transaminases increased subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	1 / 5 (20.00%) 1
Ejection fraction decreased			

subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	9	0
Blood cholesterol increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	6	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Neutrophil count decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	0	5	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Weight decreased			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			

subjects affected / exposed	3 / 12 (25.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	5	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Thyroxine decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Liver palpable			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Infusion related reaction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Muscle strain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Wound			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Pericardial effusion			

subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Left ventricular dysfunction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 8 (25.00%)	2 / 5 (40.00%)
occurrences (all)	0	2	2
Headache			
subjects affected / exposed	2 / 12 (16.67%)	4 / 8 (50.00%)	1 / 5 (20.00%)
occurrences (all)	7	4	1
Lethargy			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	1 / 5 (20.00%)
occurrences (all)	0	1	6
Neurotoxicity			
subjects affected / exposed	5 / 12 (41.67%)	3 / 8 (37.50%)	1 / 5 (20.00%)
occurrences (all)	6	3	1
Neuropathy peripheral			
subjects affected / exposed	4 / 12 (33.33%)	2 / 8 (25.00%)	1 / 5 (20.00%)
occurrences (all)	13	7	2
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	1 / 5 (20.00%)
occurrences (all)	1	3	1
Presyncope			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Dizziness			
subjects affected / exposed	3 / 12 (25.00%)	5 / 8 (62.50%)	0 / 5 (0.00%)
occurrences (all)	4	7	0
Migraine			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Neuralgia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Radicular pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Somnolence			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Parosmia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Myoclonus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Sciatica			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tremor			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ageusia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Visual field defect			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 12 (50.00%)	4 / 8 (50.00%)	1 / 5 (20.00%)
occurrences (all)	17	16	1
Neutropenia			
subjects affected / exposed	3 / 12 (25.00%)	3 / 8 (37.50%)	2 / 5 (40.00%)
occurrences (all)	20	23	4
Leukopenia			

subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Tinnitus			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Vertigo			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Ear canal erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypoacusis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Dry eye			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Photopsia			

subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	0 / 5 (0.00%) 0
Conjunctival pallor subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Visual acuity reduced subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Vitreous detachment subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	2 / 5 (40.00%) 3
Constipation subjects affected / exposed occurrences (all)	4 / 12 (33.33%) 5	1 / 8 (12.50%) 1	2 / 5 (40.00%) 4
Diarrhoea subjects affected / exposed occurrences (all)	11 / 12 (91.67%) 66	7 / 8 (87.50%) 57	5 / 5 (100.00%) 31
Dry mouth subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 8 (0.00%) 0	2 / 5 (40.00%) 2
Dyspepsia subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 2	1 / 8 (12.50%) 2	1 / 5 (20.00%) 1
Gastrointestinal sounds abnormal subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	1 / 5 (20.00%) 8
Mouth ulceration subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 2	1 / 5 (20.00%) 2
Odynophagia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 8 (0.00%) 0	1 / 5 (20.00%) 1

Nausea			
subjects affected / exposed	8 / 12 (66.67%)	5 / 8 (62.50%)	3 / 5 (60.00%)
occurrences (all)	23	6	8
Vomiting			
subjects affected / exposed	4 / 12 (33.33%)	2 / 8 (25.00%)	2 / 5 (40.00%)
occurrences (all)	17	6	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Abdominal pain			
subjects affected / exposed	1 / 12 (8.33%)	3 / 8 (37.50%)	1 / 5 (20.00%)
occurrences (all)	1	4	1
Abdominal pain upper			
subjects affected / exposed	3 / 12 (25.00%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	3	4	0
Gastrointestinal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Gingival bleeding			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Haemorrhoids			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Stomatitis			
subjects affected / exposed	2 / 12 (16.67%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	3	5	0
Colitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Rectal tenesmus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Aphthous ulcer subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Dysphagia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Flatulence subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Hepatobiliary disorders Hepatomegaly subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 2	0 / 5 (0.00%) 0
Hepatic pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Hepatocellular injury subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 8 (12.50%) 1	0 / 5 (0.00%) 0
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 6	4 / 8 (50.00%) 4	3 / 5 (60.00%) 3
Dry skin subjects affected / exposed occurrences (all)	3 / 12 (25.00%) 3	0 / 8 (0.00%) 0	2 / 5 (40.00%) 2
Nail disorder subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 8 (12.50%) 1	1 / 5 (20.00%) 1
Pruritus subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 5	2 / 8 (25.00%) 2	1 / 5 (20.00%) 1
Rash erythematous subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 5	1 / 8 (12.50%) 3	3 / 5 (60.00%) 4
Rash macular			

subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	1 / 5 (20.00%)
occurrences (all)	0	1	1
Rash maculo-papular			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	2 / 5 (40.00%)
occurrences (all)	3	0	2
Swelling face			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nail discolouration			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rash papular			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	3	0	0
Rash pruritic			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin reaction			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Melanoderma			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Nail dystrophy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Onycholysis			
subjects affected / exposed	2 / 12 (16.67%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	2	2	0

Rash			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	2	5	0
Skin hyperpigmentation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Dermatitis acneiform			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	3	0
Eczema			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Generalised erythema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Dysuria			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Proteinuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Renal failure			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Haematuria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary incontinence			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Joint swelling			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	4 / 12 (33.33%)	3 / 8 (37.50%)	2 / 5 (40.00%)
occurrences (all)	5	4	2
Muscle spasms			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	1 / 5 (20.00%)
occurrences (all)	1	5	1
Musculoskeletal pain			
subjects affected / exposed	3 / 12 (25.00%)	1 / 8 (12.50%)	1 / 5 (20.00%)
occurrences (all)	5	2	1
Arthralgia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	3	1	0
Bone pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	1	2	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Myalgia			
subjects affected / exposed	2 / 12 (16.67%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	2	3	0
Musculoskeletal discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Neck pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Pain in extremity			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	2	2	0
Osteoarthritis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0

Spinal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Flank pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Hordeolum			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	2 / 5 (40.00%)
occurrences (all)	1	0	2
Rhinitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	3 / 5 (60.00%)
occurrences (all)	1	1	3
Urinary tract infection bacterial			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	1 / 5 (20.00%)
occurrences (all)	1	0	1
Cellulitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Herpes zoster			

subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oral candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Paronychia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Fungal infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	2 / 12 (16.67%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	4	0	0
Pyelonephritis acute			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Sinusitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	1	1	0
Vaginal infection			
subjects affected / exposed	1 / 12 (8.33%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	1	1	0

Varicella			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Bacterial infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Folliculitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Herpes virus infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Rash pustular			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	5 / 12 (41.67%)	3 / 8 (37.50%)	2 / 5 (40.00%)
occurrences (all)	39	15	2
Decreased appetite			

subjects affected / exposed	4 / 12 (33.33%)	3 / 8 (37.50%)	2 / 5 (40.00%)
occurrences (all)	8	3	2
Hypertriglyceridaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 8 (25.00%)	0 / 5 (0.00%)
occurrences (all)	1	3	0
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Hypomagnesaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 8 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Calcium deficiency			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Cell death			
subjects affected / exposed	0 / 12 (0.00%)	1 / 8 (12.50%)	0 / 5 (0.00%)
occurrences (all)	0	8	0

Non-serious adverse events	Sched 2 - AZD5363 400 mg bd	Part A Schedule 2 480 mg bd	Part B AZD5363
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 7 (100.00%)	6 / 6 (100.00%)	50 / 54 (92.59%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Hypertension			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Hot flush			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 54 (3.70%)
occurrences (all)	0	1	2
Lymphoedema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	2 / 54 (3.70%)
occurrences (all)	1	1	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 7 (85.71%)	3 / 6 (50.00%)	7 / 54 (12.96%)
occurrences (all)	11	3	8
Device breakage			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	16 / 54 (29.63%)
occurrences (all)	0	0	20
Oedema peripheral			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	8 / 54 (14.81%)
occurrences (all)	3	2	10
Malaise			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 54 (7.41%)
occurrences (all)	0	0	4
Peripheral swelling			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	1	0	3
Pyrexia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	14 / 54 (25.93%)
occurrences (all)	0	3	15
Influenza like illness			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Chest pain			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Non-cardiac chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Suprapubic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Catheter site related reaction			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Hyperthermia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 54 (7.41%)
occurrences (all)	0	0	5
Reproductive system and breast disorders			
Breast discharge			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Pelvic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Vaginal discharge			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Menorrhagia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	11 / 54 (20.37%)
occurrences (all)	1	2	13
Productive cough			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	5 / 54 (9.26%)
occurrences (all)	0	0	5
Dysphonia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Dyspnoea exertional			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Dyspnoea			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	6 / 54 (11.11%)
occurrences (all)	2	1	6
Epistaxis			
subjects affected / exposed	2 / 7 (28.57%)	2 / 6 (33.33%)	5 / 54 (9.26%)
occurrences (all)	2	3	5
Nasal dryness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 54 (0.00%)
occurrences (all)	0	2	0
Nasal obstruction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 54 (7.41%)
occurrences (all)	0	1	6
Rhinorrhoea			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	2	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depressed mood			

subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Insomnia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Anxiety			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	2	0	2
Sleep disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Confusional state			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Depression			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 54 (3.70%)
occurrences (all)	0	1	2
Hallucination			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Irritability			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Ejection fraction decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	13 / 54 (24.07%)
occurrences (all)	0	0	22
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2

Aspartate aminotransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	11 / 54 (20.37%)
occurrences (all)	0	0	19
Blood cholesterol increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	6
Blood creatinine increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Neutrophil count decreased			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 54 (7.41%)
occurrences (all)	0	1	8
Lymphocyte count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Weight decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	5 / 54 (9.26%)
occurrences (all)	0	0	5
White blood cell count decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Blood glucose increased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Thyroxine decreased			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Blood bilirubin increased			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 54 (1.85%) 1
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 54 (0.00%) 0
Liver palpable subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 54 (0.00%) 0
Injury, poisoning and procedural complications Lumbar vertebral fracture subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 54 (0.00%) 0
Infusion related reaction subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	3 / 54 (5.56%) 3
Muscle strain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 54 (0.00%) 0
Wound subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 54 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 54 (1.85%) 1
Pericardial effusion subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 54 (1.85%) 1
Left ventricular dysfunction subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 6 (0.00%) 0	0 / 54 (0.00%) 0
Nervous system disorders Dysgeusia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 4	1 / 6 (16.67%) 1	11 / 54 (20.37%) 13
Headache			

subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	8 / 54 (14.81%)
occurrences (all)	2	1	14
Lethargy			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	2 / 54 (3.70%)
occurrences (all)	0	3	5
Neurotoxicity			
subjects affected / exposed	3 / 7 (42.86%)	2 / 6 (33.33%)	5 / 54 (9.26%)
occurrences (all)	3	3	9
Neuropathy peripheral			
subjects affected / exposed	2 / 7 (28.57%)	1 / 6 (16.67%)	13 / 54 (24.07%)
occurrences (all)	3	1	22
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	14 / 54 (25.93%)
occurrences (all)	0	0	17
Paraesthesia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	6 / 54 (11.11%)
occurrences (all)	1	2	8
Presyncope			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Dizziness			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	1 / 54 (1.85%)
occurrences (all)	0	3	1
Migraine			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Neuralgia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Radicular pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	1 / 54 (1.85%)
occurrences (all)	0	1	1
Parosmia			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Myoclonus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Tremor			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	4	0
Ageusia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Visual field defect			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	18 / 54 (33.33%)
occurrences (all)	0	2	32
Neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	7 / 54 (12.96%)
occurrences (all)	0	0	21
Leukopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	5 / 54 (9.26%)
occurrences (all)	0	0	16
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Febrile neutropenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Thrombocytopenia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0

Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	2
Tinnitus			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	8
Vertigo			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Ear canal erythema			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Hypoacusis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	2	1	0
Dry eye			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	2 / 54 (3.70%)
occurrences (all)	0	2	2
Photopsia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Conjunctival pallor			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Visual acuity reduced			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Vitreous detachment			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Constipation			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	6 / 7 (85.71%)	6 / 6 (100.00%)	41 / 54 (75.93%)
occurrences (all)	34	101	228
Dry mouth			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 54 (1.85%)
occurrences (all)	2	1	1
Dyspepsia			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	5 / 54 (9.26%)
occurrences (all)	1	1	6
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Mouth ulceration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 54 (7.41%)
occurrences (all)	0	0	5
Odynophagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	2 / 7 (28.57%)	5 / 6 (83.33%)	21 / 54 (38.89%)
occurrences (all)	5	15	33
Vomiting			
subjects affected / exposed	2 / 7 (28.57%)	4 / 6 (66.67%)	14 / 54 (25.93%)
occurrences (all)	2	9	20
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Toothache			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	4 / 54 (7.41%)
occurrences (all)	1	0	6

Abdominal pain			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	2 / 54 (3.70%)
occurrences (all)	0	2	4
Abdominal pain upper			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	5 / 54 (9.26%)
occurrences (all)	2	0	6
Gastrointestinal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gingival bleeding			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Haemorrhoids			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	15 / 54 (27.78%)
occurrences (all)	2	10	26
Colitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Rectal tenesmus			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Aphthous ulcer			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Dysphagia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Flatulence			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hepatomegaly			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Hepatic pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Hepatocellular injury			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	28 / 54 (51.85%)
occurrences (all)	2	0	28
Dry skin			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 54 (7.41%)
occurrences (all)	0	1	5
Nail disorder			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	4
Pruritus			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	2 / 54 (3.70%)
occurrences (all)	0	3	2
Rash erythematous			
subjects affected / exposed	0 / 7 (0.00%)	3 / 6 (50.00%)	3 / 54 (5.56%)
occurrences (all)	0	5	3
Rash macular			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 54 (7.41%)
occurrences (all)	0	1	8
Rash maculo-papular			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	14 / 54 (25.93%)
occurrences (all)	2	0	18
Swelling face			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Nail discolouration			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	4 / 54 (7.41%)
occurrences (all)	0	1	4
Rash papular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	8
Rash pruritic			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	1	0	3
Skin reaction			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	5
Erythema			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	2 / 54 (3.70%)
occurrences (all)	1	1	4
Melanoderma			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Nail dystrophy			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Onycholysis			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	2	0	2
Rash			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	8 / 54 (14.81%)
occurrences (all)	1	0	8
Skin hyperpigmentation			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	2	0
Dermatitis acneiform			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Eczema			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	0 / 54 (0.00%) 0
Generalised erythema subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 2	0 / 54 (0.00%) 0
Renal and urinary disorders			
Acute kidney injury subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	1 / 54 (1.85%) 1
Dysuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	3 / 54 (5.56%) 4
Proteinuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	3 / 54 (5.56%) 3
Renal failure subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 54 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	2 / 6 (33.33%) 2	1 / 54 (1.85%) 1
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	1 / 54 (1.85%) 2
Musculoskeletal and connective tissue disorders			
Joint swelling subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 6 (0.00%) 0	0 / 54 (0.00%) 0
Back pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	1 / 6 (16.67%) 1	8 / 54 (14.81%) 10
Muscle spasms subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 6 (16.67%) 1	3 / 54 (5.56%) 6
Musculoskeletal pain			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	6 / 54 (11.11%)
occurrences (all)	0	1	7
Arthralgia			
subjects affected / exposed	1 / 7 (14.29%)	2 / 6 (33.33%)	7 / 54 (12.96%)
occurrences (all)	1	2	8
Bone pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Myalgia			
subjects affected / exposed	3 / 7 (42.86%)	0 / 6 (0.00%)	5 / 54 (9.26%)
occurrences (all)	5	0	6
Musculoskeletal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Neck pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Osteoarthritis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Spinal pain			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Flank pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Groin pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			

Hordeolum			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	7 / 54 (12.96%)
occurrences (all)	0	0	11
Rhinitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	7 / 54 (12.96%)
occurrences (all)	0	1	13
Urinary tract infection bacterial			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	1 / 54 (1.85%)
occurrences (all)	2	2	1
Cellulitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Cystitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	4
Herpes zoster			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Oral candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 54 (7.41%)
occurrences (all)	0	0	5
Paronychia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	4 / 54 (7.41%)
occurrences (all)	0	0	4
Oral herpes			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	6

Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	8 / 54 (14.81%)
occurrences (all)	0	0	12
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	3 / 54 (5.56%)
occurrences (all)	0	0	3
Fungal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Pyelonephritis acute			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Sinusitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	0 / 54 (0.00%)
occurrences (all)	0	4	0
Vaginal infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Varicella			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	0	0	2
Bacterial infection			
subjects affected / exposed	1 / 7 (14.29%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	1	1	0
Conjunctivitis			

subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	2 / 54 (3.70%)
occurrences (all)	1	0	2
Folliculitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	1
Viral infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	1	0	2
Herpes virus infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Rash pustular			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 54 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	15 / 54 (27.78%)
occurrences (all)	1	0	48
Decreased appetite			
subjects affected / exposed	2 / 7 (28.57%)	3 / 6 (50.00%)	10 / 54 (18.52%)
occurrences (all)	2	3	11
Hypertriglyceridaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	6 / 54 (11.11%)
occurrences (all)	0	0	8
Hypocalcaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	1 / 54 (1.85%)
occurrences (all)	0	0	1
Hypokalaemia			

subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	3 / 54 (5.56%)
occurrences (all)	0	1	3
Hypomagnesaemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Hypercholesterolaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	1	0	0
Hyponatraemia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Calcium deficiency			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0
Cell death			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 54 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 55 (87.27%)		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	10		
Hot flush			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Lymphoedema			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	16		
Device breakage			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	11 / 55 (20.00%)		
occurrences (all)	14		
Oedema peripheral			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	11		
Malaise			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	8		
Peripheral swelling			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Chest pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Non-cardiac chest pain			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Suprapubic pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Catheter site related reaction			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		

Face oedema subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Hyperthermia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0		
Immune system disorders Drug hypersensitivity subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 3		
Reproductive system and breast disorders Breast discharge subjects affected / exposed occurrences (all) Pelvic pain subjects affected / exposed occurrences (all) Vaginal discharge subjects affected / exposed occurrences (all) Menorrhagia subjects affected / exposed occurrences (all)	0 / 55 (0.00%) 0 0 / 55 (0.00%) 0 0 / 55 (0.00%) 0 0 / 55 (0.00%) 0		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all)	8 / 55 (14.55%) 11 2 / 55 (3.64%) 2 0 / 55 (0.00%) 0 2 / 55 (3.64%) 2		

Dyspnoea			
subjects affected / exposed	9 / 55 (16.36%)		
occurrences (all)	14		
Epistaxis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nasal dryness			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Nasal obstruction			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Rhinorrhoea			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Rhinitis allergic			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Insomnia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Anxiety			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Sleep disorder			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Confusional state			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Hallucination			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Irritability			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Ejection fraction decreased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Blood cholesterol increased			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Blood creatinine increased			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Gamma-glutamyltransferase increased			

subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	4		
Neutrophil count decreased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	5		
Lymphocyte count decreased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
White blood cell count decreased			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	18		
Blood glucose increased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Thyroxine decreased			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Liver palpable			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			

subjects affected / exposed 0 / 55 (0.00%) occurrences (all) 0			
Infusion related reaction subjects affected / exposed 0 / 55 (0.00%) occurrences (all) 0			
Muscle strain subjects affected / exposed 0 / 55 (0.00%) occurrences (all) 0			
Wound subjects affected / exposed 0 / 55 (0.00%) occurrences (all) 0			
Cardiac disorders Palpitations subjects affected / exposed 1 / 55 (1.82%) occurrences (all) 1 Pericardial effusion subjects affected / exposed 0 / 55 (0.00%) occurrences (all) 0 Left ventricular dysfunction subjects affected / exposed 0 / 55 (0.00%) occurrences (all) 0			
Nervous system disorders Dysgeusia subjects affected / exposed 7 / 55 (12.73%) occurrences (all) 8 Headache subjects affected / exposed 10 / 55 (18.18%) occurrences (all) 12 Lethargy subjects affected / exposed 2 / 55 (3.64%) occurrences (all) 2 Neurotoxicity subjects affected / exposed 3 / 55 (5.45%) occurrences (all) 3 Neuropathy peripheral			

subjects affected / exposed	18 / 55 (32.73%)		
occurrences (all)	26		
Peripheral sensory neuropathy			
subjects affected / exposed	10 / 55 (18.18%)		
occurrences (all)	11		
Paraesthesia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Presyncope			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Migraine			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Neuralgia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Radicular pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Somnolence			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Parosmia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Myoclonus			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Tremor			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Ageusia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Visual field defect			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	20		
Neutropenia			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	26		
Leukopenia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Febrile neutropenia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	3		
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Vertigo			

subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Ear canal erythema			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Hypoacusis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Eye disorders			
Lacrimation increased			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Dry eye			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Photopsia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Conjunctival pallor			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Visual acuity reduced			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Vitreous detachment			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	7 / 55 (12.73%)		
occurrences (all)	8		
Diarrhoea			

subjects affected / exposed	15 / 55 (27.27%)		
occurrences (all)	32		
Dry mouth			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Dyspepsia			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	8		
Gastrointestinal sounds abnormal			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Mouth ulceration			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Odynophagia			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	13 / 55 (23.64%)		
occurrences (all)	19		
Vomiting			
subjects affected / exposed	8 / 55 (14.55%)		
occurrences (all)	10		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		
Abdominal pain upper			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Gastrointestinal pain			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Gingival bleeding			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Haemorrhoids			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Stomatitis			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Colitis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Rectal tenesmus			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Aphthous ulcer			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Flatulence			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hepatomegaly			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hepatic pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Hepatocellular injury			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	27 / 55 (49.09%)		
occurrences (all)	30		
Dry skin			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Nail disorder			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	7		
Rash erythematous			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
Rash macular			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Swelling face			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Nail discolouration			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Palmar-plantar erythrodysesthesia syndrome			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Rash papular			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Rash pruritic			

subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Skin reaction			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Erythema			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	4		
Melanoderma			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Nail dystrophy			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Onycholysis			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	8		
Skin hyperpigmentation			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Dermatitis acneiform			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Generalised erythema			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		

Dysuria			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Proteinuria			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Haematuria			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Urinary incontinence			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Back pain			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Muscle spasms			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	7		
Arthralgia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	12		
Bone pain			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Musculoskeletal chest pain			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	12 / 55 (21.82%)		
occurrences (all)	24		
Musculoskeletal discomfort			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Neck pain			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	5		
Osteoarthritis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Spinal pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Flank pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Groin pain			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Hordeolum			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Gastroenteritis viral			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Nasopharyngitis			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	7		

Rhinitis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Urinary tract infection bacterial			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Cellulitis			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Cystitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Oral candidiasis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Paronychia			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Oral herpes			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	6		
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Fungal infection			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		

Influenza			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
Pyelonephritis acute			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection bacterial			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Vaginal infection			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Varicella			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Bacterial infection			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Conjunctivitis			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Folliculitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Viral infection			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Herpes virus infection			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	2		
Rash pustular			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	13		
Decreased appetite			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Hypertriglyceridaemia			
subjects affected / exposed	5 / 55 (9.09%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	3 / 55 (5.45%)		
occurrences (all)	4		
Hypokalaemia			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	11		
Hypomagnesaemia			
subjects affected / exposed	4 / 55 (7.27%)		
occurrences (all)	6		
Hypercholesterolaemia			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Hyponatraemia			

subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Calcium deficiency			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		
Cell death			
subjects affected / exposed	0 / 55 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2012	Reporting time of an SAE was updated from "within 1 day ie, immediately but no later than the end of the next business day" to "immediately or no later than 24 hours of when investigator became aware of it".
24 April 2013	Replacement of AZD5363 continuous dosing schedule with an intermittent dosing schedule. The total number of patients to be enrolled was changed from 60 to 100 and primary endpoint changed to PFS. Addition of OS as a secondary endpoint. Extension of WHO PS evaluations. Introduction of an independent SRC Provision for a change in AZD5363/placebo formulation: During Part A, patients could receive AZD5363 in capsule form only. During Part B, patients could receive AZD5363/placebo as capsules or as dose-equivalent tablets. A tablet formulation could be applied in all sites or in selected sites only. Inclusion of Japanese patient population in the study.
09 May 2013	Part B inclusion criteria: Requirement for patients to be negative for presence of HER2 was added for entry to Part B of this study Part B inclusion criteria: Removal of requirement for patients to have received prior endocrine therapy for entry to Part B Updated exclusion criteria 9 Part B patient stratification updated Efficacy variable: DRR added as a new efficacy variable Part B patient assessments: Reduction in the number of patient assessments and the number of days on which patients were required to attend for evaluation Data Monitoring Committee: Inclusion of an AstraZeneca internal Data Monitoring Committee
29 April 2015	Doses and treatment regimens: changes were made to the text to permit the use of dose-equivalent tablets in Part A of the study, as the previous wording specified capsules only Part B Patient Assessments: changes made to, and an overall reduction in, the number of patient assessments and the number of days on which patients were required to attend clinic for evaluation Exclusion criteria: updated exclusion criterion 4 and removal of exclusion criterion 11 Part A and B secondary objectives: addition of the secondary objective to assess the toxicity burden associated with diarrhoea Update to exploratory objectives Update to the Asian patient evaluation Update to Part B inclusion criterion 1 Update to exclusion criterion 20 Treatment description updated

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.

QoL, PK/PD & efficacy response modelling were considered non-key secondary endpoints and not disclosed at this time. QoL data was limited and considered exploratory, PK/PD and modelling were not reported in CSR. Diarrhoea burden is reported with AEs.

Notes: