Clinical trial results:
PARAGON: Phase II study of aromatase inhibitors in women with potentially hormone responsive recurrent/metastatic gynaecological neoplasms

Summary

EudraCT number	2011-000501-52
Trial protocol	GB
Global end of trial date	30 April 2020

Results information

Result version number	v1 (current)
This version publication date	20 May 2021
First version publication date	20 May 2021

Trial information

Trial identification

Sponsor protocol code	PARAGON2011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Australian New Zealand Clinical Trials Registry: ACTRN12610000796088

Notes:

Sponsors

Sponsor organisation name	NHS Greater Glasgow & Clyde and University of Glasgow
Sponsor organisation address	NHS Greater Glasgow & Clyde Research & Innovation, Ward 11, Dykebar hospital, Grahamston Road, Paisley, United Kingdom, PA2 7DE
Public contact	Laura Alexander, Project Manager, Cancer Research UK Clinical Trials Unit, +44 01413017212, laura.alexander@glasgow.ac.uk
Scientific contact	Laura Alexander, Project Manager, Cancer Research UK Clinical Trials Unit, +44 01413017212, laura.alexander@glasgow.ac.uk
Sponsor organisation name	University of Sydney
Sponsor organisation address	Locked Bag 77, Camperdown, Australia, 2050
Public contact	Nathan Bradshaw, University of Sydney, 61 295625000, paragon@ctc.usyd.edu.au
Scientific contact	Nathan Bradshaw, University of Sydney, 61 295625000, paragon@ctc.usyd.edu.au

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	11 March 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2020
Global end of trial reached?	Yes
Global end of trial date	30 April 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The principal objective of the study is clinical benefit rate determined by the proportion of patients experiencing either stable disease or response within 3 months of commencing treatment.

Protection of trial subjects:

As the study drug (anastrozole) lowers circulating oestrogen levels it may cause a reduction in bone mineral density (thinning of the bones) which in some people may put them at an increased risk of broken bones (fractures). Women who have or are at risk of severe bone thinning (osteoporosis) may have their bone mineral density formally assessed by a special type of scan called bone densitometry (DEXA) before they start treatment and at 1-2 year intervals depending on the findings. For this reason it is recommended, that a DEXA scan of hip, femoral neck or lumbar spine be performed within 12 months of registration to this trial for each patient and the need for a scan will be decided by your treating doctor.

Anastrozole is not recommended for use in premenopausal women as safety and efficacy have not been established. Women with child bearing potential will not be included in this trial.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	01 August 2011
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	Australia: 206
Country: Number of subjects enrolled	New Zealand: 12
Country: Number of subjects enrolled	United Kingdom: 96
Country: Number of subjects enrolled	Belgium: 17
Worldwide total number of subjects	331
EEA total number of subjects	17

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)	167
From 65 to 84 years	164
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Women with oestrogen receptor and/or progesterone receptor positive (ER/PR+ve) potentially hormone responsive recurrent or metastatic gynaecological cancers including selected patients with epithelial ovarian cancer, endometrial cancers, miscellaneous sarcomas and sex cord stromal tumours of the ovary

Pre-assignment

Screening details:

Patients with recurrent or metastatic gynaecological cancer with previous primary tumour diagnosis confirmed histologically.
All patients will have central review and analyses of ER/PR at a later date to confirm receptor status, but entry to the study will be based on hormone receptor positivity according to local hormone receptor analyses.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Single Arm

Arm description:

Single Arm study

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

Dosage and administration details:

1 tabley (1mg) taken orally once a day

Number of subjects in period 1	Single Arm
Started	331
Treatment	331
Completed	331

Baseline characteristics

Reporting groups	
Reporting group title	Single Arm
Reporting group description:	
Single Arm study	

Reporting group values	Single Arm	Total	
Number of subjects	331	331	
Age categorical Units: Subjects			
Adults (18-64 years)	167	167	
From 65-84 years	160	160	
85 years and over	4	4	
Age continuous Units: years			
arithmetic mean	63.79		
standard deviation	± 11.17	-	
Gender categorical Units: Subjects			
Female	331	331	
Male	0	0	

Subject analysis sets	
Subject analysis set title	Endometrial Stroma Sarcoma
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with low-grade endometrial stromal sarcomas	
Subject analysis set title	PRROC
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with Estrogen or Progesterone Receptor- Positive Platinum-Resistant or -Refractory Recurrent Ovarian Cancer	
Subject analysis set title	CA125
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Asymptomatic patients with estrogen and progesterone receptor-positive recurrent ovarian cancer and CA125 progression	
Subject analysis set title	Endometrial Cancer
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer	
Subject analysis set title	Low Grade Ovarian
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with estrogen receptor-positive recurrent/metastatic low-grade ovarian cancers and serous borderline ovarian tumors	
Subject analysis set title	Granulosa Cell Tumour
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with metastatic granulosa cell tumours

Subject analysis set title	Metastatic Leiomyosarcoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with recurrent/metastatic leimoyosarcoma

Subject analysis set title	Uterine Carcinosarcoma
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with recurrent/metastatic uterine carcinosarcoma(UCS)

Reporting group values	Endometrial Stroma Sarcoma	PRROC	CA125
Number of subjects	15	49	52
Age categorical Units: Subjects			
Adults (18-64 years)	12	25	35
From 65-84 years	9	28	21
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	61.63	65.08	65.40
standard deviation	± 9.92	± 9.43	± 10.36
Gender categorical Units: Subjects			
Female	15	49	52
Male	0	0	0

Reporting group values	Endometrial Cancer	Low Grade Ovarian	Granulosa Cell Tumour
Number of subjects	82	36	39
Age categorical Units: Subjects			
Adults (18-64 years)	27	23	28
From 65-84 years	57	14	12
85 years and over	3	0	0
Age continuous Units: years			
arithmetic mean	68.23	57.19	59.60
standard deviation	± 8.79	± 16.09	± 9.65
Gender categorical Units: Subjects			
Female	82	36	39
Male	0	0	0

Reporting group values	Metastatic Leiomyosarcoma	Uterine Carcinosarcoma	
Number of subjects	32	7	
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: years arithmetic mean standard deviation	± 	± 	
Gender categorical Units: Subjects			
Female Male	 	 	

End points

End points reporting groups

Reporting group title	Single Arm
Reporting group description: Single Arm study	
Subject analysis set title	Endometrial Stroma Sarcoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with low-grade endometrial stromal sarcomas	
Subject analysis set title	PRROC
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with Estrogen or Progesterone Receptor- Positive Platinum-Resistant or -Refractory Recurrent Ovarian Cancer	
Subject analysis set title	CA125
Subject analysis set type	Sub-group analysis
Subject analysis set description: Asymptomatic patients with estrogen and progesterone receptor-positive recurrent ovarian cancer and CA125 progression	
Subject analysis set title	Endometrial Cancer
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with recurrent estrogen (ER)/progesterone (PR) positive endometrial cancer	
Subject analysis set title	Low Grade Ovarian
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with estrogen receptor-positive recurrent/metastatic low-grade ovarian cancers and serous borderline ovarian tumors	
Subject analysis set title	Granulosa Cell Tumour
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with metastatic granulosa cell tumours	
Subject analysis set title	Metastatic Leiomyosarcoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with recurrent/metastatic leimoyosarcoma	
Subject analysis set title	Uterine Carcinosarcoma
Subject analysis set type	Sub-group analysis
Subject analysis set description: Patients with recurrent/metastatic uterine carcinosarcoma(UCS)	

Primary: Clinical Benefit Rate (Proportion of patients with Stable Disease or Response)

End point title	Clinical Benefit Rate (Proportion of patients with Stable Disease or Response)
End point description: Clinical benefit rate as determined by the proportion of patients experiencing either stable disease or response within 3 months of commencing treatment.	
End point type	Primary
End point timeframe: Within 3 months of commencing treatment	

End point values	Endometrial Stroma Sarcoma	PRROC	CA125	Endometrial Cancer
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	15	49	52	82
Units: Number of patients	11	13	18	36

End point values	Low Grade Ovarian	Granulosa Cell Tumour	Metastatic Leiomyosarcoma	Uterine Carcinosarcoma
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	36	39	32	7
Units: Number of patients	23	32	11	3

Statistical analyses

Statistical analysis title	Kaplan-Meier

Statistical analysis description:

Analysis was performed using the proportion of patients who responded/experienced clinical benefit together with 95% confidence interval for the estimates. Comparisons were two-tailed and a nominal significance level of 0.05 was applied. nalysed using tusing time-to-event methods, with Kaplan-Meier survival curves constructed for graphical display and unadjusted log-rank tests performed where appropriate. 95% CIs for proportions were constructed using the Wilson method

Comparison groups	PRROC v CA125
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	t-test, 2-sided

Notes:

[1] - Single arm, phase 2,

Secondary: Progression free survival

End point title	Progression free survival

End point description:

End point type	Secondary

End point timeframe:

Progression free survival

End point values	Endometrial Stroma Sarcoma	PRROC	CA125	Endometrial Cancer
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[2]	49	52	82
Units: Average months of PFS				
median (confidence interval 95%)	(to)	2.7 (2.0 to 2.8)	2.7 (2.1 to 3.1)	3.2 (2.8 to 5.4)

Notes:

[2] - Median PFS was not reached

End point values	Low Grade Ovarian	Granulosa Cell Tumour	Metastatic Leiomyosarcoma	Uterine Carcinosarcoma
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	36	39	32	7
Units: Average months of PFS				
median (confidence interval 95%)	11.1 (3.2 to 11.9)	8.6 (5.5 to 13.5)	2.8 (2.6 to 4.9)	2.7 (1.1 to 8.2)

Statistical analyses

Statistical analysis title	Kaplan-Meier

Statistical analysis description:

Time-to-event analyses will be described with Kaplan-Meier curves and, where appropriate unadjusted logrank tests will be performed. Death from any cause will be considered as an event.

Comparison groups	Endometrial Cancer v CA125
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.05
Method	t-test, 2-sided

Notes:

[3] - Single arm, phase 2 trial

Secondary: Duration of Response

End point title	Duration of Response

End point description:

End point type	Secondary

End point timeframe:

Duration of response in each subgroup

End point values	Endometrial Stroma Sarcoma	PRROC	CA125	Endometrial Cancer
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[4]	49	52	82
Units: Average number of months				
median (confidence interval 95%)	(to)	2.8 (2.6 to 5.7)	6.5 (2.8 to 11.7)	5.6 (3.0 to 13.7)

Notes:

[4] - only 1 patient progressed (at 13 months after achieving benefit) so a median could not be estimated.

End point values	Low Grade Ovarian	Granulosa Cell Tumour	Metastatic Leiomyosarcoma	Uterine Carcinosarcoma
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	36	39		
Units: Average number of months				
median (confidence interval 95%)	9.5 (8.3 to 25.8)	8.4 (4.3 to 14.8)	5.8 (2.2 to 58.3)	5.6 (2.5 to 5.7)

Statistical analyses

Statistical analysis title	Kaplan-Meier

Statistical analysis description:

duration of clinical benefit were analysed using time-to-event methods, with Kaplan-Meier survival curves constructed for graphical display and unadjusted log-rank tests performed where appropriate. Death from any cause was considered an event.

Comparison groups	PRROC v CA125 v Endometrial Cancer v Low Grade Ovarian
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	t-test, 1-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline SAEs are reported up to 30 days from the end of study drug administration.	
Adverse event reporting additional description:	
Once a month for the first 3 months, 3-monthly until progression.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Reporting groups	
Reporting group title	Single Arm
Reporting group description:	
Single Arm study	

Serious adverse events	Single Arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 331 (20.24%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Gastric Outlet Obstruction			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chest Pain			

subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertension			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Abdominal Pain			
subjects affected / exposed	8 / 331 (2.42%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thromboembolic Event			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Hypomagnesaemia				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Vaginal Haemorrhage				
subjects affected / exposed	4 / 331 (1.21%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Upper gastrointestinal haemorrhage				
subjects affected / exposed	2 / 331 (0.60%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bowel obstruction				
subjects affected / exposed	6 / 331 (1.81%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorder				
subjects affected / exposed	3 / 331 (0.91%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 331 (0.30%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Respiratory, thoracic and mediastinal disorders			
Chest Infection			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung infection			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary Incontinence			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	5 / 331 (1.51%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Creatine urine increased			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cholelithiasis			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Kidney infection			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pelvic pain			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neck pain			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Constipation			
subjects affected / exposed	4 / 331 (1.21%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 331 (0.60%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Diarrhoea			
subjects affected / exposed	1 / 331 (0.30%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Single Arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	286 / 331 (86.40%)		
Vascular disorders			
Raynaud's phenomenon			
subjects affected / exposed	12 / 331 (3.63%)		
occurrences (all)	25		
General disorders and administration site conditions			
Headache			
subjects affected / exposed	68 / 331 (20.54%)		
occurrences (all)	158		
Fatigue			
subjects affected / exposed	200 / 331 (60.42%)		
occurrences (all)	635		
Alopecia			
subjects affected / exposed	33 / 331 (9.97%)		
occurrences (all)	64		
Pain			
subjects affected / exposed	21 / 331 (6.34%)		
occurrences (all)	34		
Abdominal pain			
subjects affected / exposed	96 / 331 (29.00%)		
occurrences (all)	160		
Back pain			
subjects affected / exposed	22 / 331 (6.65%)		
occurrences (all)	48		
Immune system disorders			
Raynaud's phenomenon			

subjects affected / exposed	11 / 331 (3.32%)		
occurrences (all)	25		
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	13 / 331 (3.93%)		
occurrences (all)	27		
Vaginal dryness			
subjects affected / exposed	48 / 331 (14.50%)		
occurrences (all)	162		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 331 (7.25%)		
occurrences (all)	38		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 331 (2.72%)		
occurrences (all)	23		
Insomnia			
subjects affected / exposed	32 / 331 (9.67%)		
occurrences (all)	54		
Depression			
subjects affected / exposed	6 / 331 (1.81%)		
occurrences (all)	15		
Cardiac disorders			
Hypertension			
subjects affected / exposed	16 / 331 (4.83%)		
occurrences (all)	33		
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	8 / 331 (2.42%)		
occurrences (all)	26		
Myalgia			
subjects affected / exposed	11 / 331 (3.32%)		
occurrences (all)	20		
Peripheral sensory neuropathy			

subjects affected / exposed	36 / 331 (10.88%)		
occurrences (all)	80		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	12 / 331 (3.63%)		
occurrences (all)	16		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	21 / 331 (6.34%)		
occurrences (all)	21		
Abdominal pain			
subjects affected / exposed	131 / 331 (39.58%)		
occurrences (all)	85		
Reflux gastritis			
subjects affected / exposed	12 / 331 (3.63%)		
occurrences (all)	25		
Vomiting			
subjects affected / exposed	49 / 331 (14.80%)		
occurrences (all)	61		
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	9 / 331 (2.72%)		
occurrences (all)	22		
Hot flush	Additional description: AKA Hot Flashes		
subjects affected / exposed	22 / 331 (6.65%)		
occurrences (all)	25		
Rash			
subjects affected / exposed	41 / 331 (12.39%)		
occurrences (all)	63		
Renal and urinary disorders			
Urinary incontinence			
subjects affected / exposed	13 / 331 (3.93%)		
occurrences (all)	19		
Endocrine disorders			
Abnormal Lipids			
subjects affected / exposed	27 / 331 (8.16%)		
occurrences (all)	55		

Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	4 / 331 (1.21%)		
occurrences (all)	15		
Neuropathy peripheral			
subjects affected / exposed	53 / 331 (16.01%)		
occurrences (all)	81		
Dyspnoea			
subjects affected / exposed	16 / 331 (4.83%)		
occurrences (all)	33		
Arthralgia			
subjects affected / exposed	171 / 331 (51.66%)		
occurrences (all)	506		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	69 / 331 (20.85%)		
occurrences (all)	112		
Nausea			
subjects affected / exposed	107 / 331 (32.33%)		
occurrences (all)	193		
Constipation			
subjects affected / exposed	67 / 331 (20.24%)		
occurrences (all)	124		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2012	inclusion of the Granulosa Cell Subgroup Study which requires the collection of blood from patients should they consent to participateI

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.

N/A

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31130288

http://www.ncbi.nlm.nih.gov/pubmed/31227223

http://www.ncbi.nlm.nih.gov/pubmed/31328463

http://www.ncbi.nlm.nih.gov/pubmed/28498256

http://www.ncbi.nlm.nih.gov/pubmed/33608144