Clinical trial results:
Phase II window of opportunity study of short term preoperative treatment with enzalutamide (alone or in combination with exemestane) in patients with primary breast cancer.

Summary

EudraCT number	2014-002001-37
Trial protocol	GB ES DE
Global end of trial date	31 March 2020

Results information

Result version number	v1 (current)
This version publication date	15 May 2021
First version publication date	15 May 2021

Trial information

Trial identification

Sponsor protocol code	009684QM

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02676986
WHO universal trial number (UTN)	-
Other trial identifiers	Not applicable: Not applicable

Notes:

Sponsors

Sponsor organisation name	Queen Mary University of London
Sponsor organisation address	Mile End Road, London, United Kingdom, E1 4NS
Public contact	CECM Trials Team, Queen Mary University of London, +44 2078828197, bci-cecmmonitoring@qmul.ac.uk
Scientific contact	CECM Trials Team, Queen Mary University of London, +44 2078828197, bci-cecmmonitoring@qmul.ac.uk

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	23 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2020
Global end of trial reached?	Yes
Global end of trial date	31 March 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Determine the ability of enzalutamide, when taken alone or in combination with exemestane, to affect the growth of cancer cells in patients with newly diagnosed breast cancer.

Protection of trial subjects:

The study design aimed to minimise potential risks. Eligibility criteria were selected to enhance the safety of patients in this trial and a number of exclusion criteria were specifically based on the known safety profiles of the study drug treatments. Short-term preoperative 'window' studies of 2-4 weeks treatment are a validated strategy to provide rapid and cost-efficient proof-of-concept for novel treatment approaches by assessing the direct effects of the study treatment on the tumour tissue.

Background therapy:

None

Evidence for comparator:

The ER+ve cohort focused on postmenopausal women with newly diagnosed, untreated ER+ve, invasive primary breast cancer. In this cohort, the trial evaluated the effects of preoperative therapy with enzalutamide plus exemestane relative to exemestane alone. It was established practice to treat ER-positive patients with endocrine therapy as soon as the diagnosis of breast cancer has been established, and several clinical trials had shown that two weeks preoperative therapy with an AI or tamoxifen markedly reduces proliferation as measured by Ki67 in human breast cancer. Experimental evidence furthermore suggests that short duration endocrine therapy shortly before and immediately after breast cancer surgery might improve long term outcome with no additional toxicity or resource implications.

For TNBC, data for short-term preoperative therapy was less established due to the lack of a targeted treatment strategy with a favourable toxicity profile. In this context enzalutamide was offered as the only drug given to investigate the effects of enzalutamide alone.

Actual start date of recruitment	22 September 2015
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	Spain: 24
Country: Number of subjects enrolled	United Kingdom: 64
Country: Number of subjects enrolled	Germany: 124
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	219
EEA total number of subjects	212

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)	105
From 65 to 84 years	110
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

From September 2015 to November 2017, 194 patients with newly diagnosed, untreated ER+ve, invasive primary breast cancer were recruited and 27 patients were recruited to the AR+ve, triple negative breast cancer cohort. In total, 221 patients were enrolled but 219 patients received treatment and were therefore included in the result analysis.

Pre-assignment

Screening details:

The ER+ve cohort focused on postmenopausal women with newly diagnosed, untreated ER+ve, invasive primary breast cancer.
The AR+ve, TNBC cohort focused on women with newly diagnosed, untreated, AR+ve, TNBC invasive primary breast cancer.
All patients had to have been previously untreated, a tumour size over 1cm, ECOG performance status 0-2.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	ER+ve Cohort Exemestane Only

Arm description:

Patients were given 25mg/day of exemestane for a minimum of 15 days and a maximum of 29 days until patients either had definitive surgery or primary medical treatment.

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

Dosage and administration details:

25 mg in 1 tablet (25 mg)

Arm title	ER+ve Cohort Enzalutamide and Exemestane

Arm description:

Patients were treated with 160mg/day of enzalutamide plus 50mg of exemestane for a minimum of 15 days and a maximum of 29 days before patients either had definitive surgery or primary medical treatment.

Arm type	Active comparator
Investigational medicinal product name	Enzalutamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

160mg/day

Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

50 mg in 2 tablets (25 mg each)

Arm title	AR+ve, TNBC

Arm description:

The AR+ve, TNBC cohort included patients with newly diagnosed, untreated, AR+ve, TNBC invasive primary breast cancer. In this cohort, the trial evaluated the effects of preoperative therapy with enzalutamide alone.

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

Dosage and administration details:

160mg/day of enzalutamide

Number of subjects in period 1	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC
Started	63	129	27
Completed	59	122	26
Not completed	4	7	1
Consent withdrawn by subject	3	1	1
Adverse event, non-fatal	1	4	-
Protocol deviation	-	2	-

Baseline characteristics

Reporting groups	
Reporting group title	ER+ve Cohort Exemestane Only
Reporting group description:	
Patients were given 25mg/day of exemestane for a minimum of 15 days and a maximum of 29 days until patients either had definitive surgery or primary medical treatment.	
Reporting group title	ER+ve Cohort Enzalutamide and Exemestane
Reporting group description:	
Patients were treated with 160mg/day of enzalutamide plus 50mg of exemestane for a minimum of 15 days and a maximum of 29 days before patients either had definitive surgery or primary medical treatment.	
Reporting group title	AR+ve, TNBC
Reporting group description:	
The AR+ve, TNBC cohort included patients with newly diagnosed, untreated, AR+ve, TNBC invasive primary breast cancer. In this cohort, the trial evaluated the effects of preoperative therapy with enzalutamide alone.	

Reporting group values	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC
Number of subjects	63	129	27
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	28	61	16
From 65-84 years	34	65	11
85 years and over	1	3	0
Age continuous Units: years			
median	66	65	60
full range (min-max)	52 to 86	49 to 87	44 to 78
Gender categorical Units: Subjects			
Female	63	129	27
Male	0	0	0
Tumour Grade Units: Subjects			
Grade 1	7	18	1
Grade 2	46	87	12
Grade 3	10	24	14
ECOG Performance Status Units: Subjects			
0 - Fully active	58	119	26
1 - Ambulatory	5	10	1

Reporting group values	Total		
Number of subjects	219		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	105		
From 65-84 years	110		
85 years and over	4		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	219		
Male	0		
Tumour Grade Units: Subjects			
Grade 1	26		
Grade 2	145		
Grade 3	48		
ECOG Performance Status Units: Subjects			
0 - Fully active	203		
1 - Ambulatory	16		

End points

End points reporting groups

Reporting group title	ER+ve Cohort Exemestane Only
Reporting group description:	
Patients were given 25mg/day of exemestane for a minimum of 15 days and a maximum of 29 days until patients either had definitive surgery or primary medical treatment.	
Reporting group title	ER+ve Cohort Enzalutamide and Exemestane
Reporting group description:	
Patients were treated with 160mg/day of enzalutamide plus 50mg of exemestane for a minimum of 15 days and a maximum of 29 days before patients either had definitive surgery or primary medical treatment.	
Reporting group title	AR+ve, TNBC
Reporting group description:	
The AR+ve, TNBC cohort included patients with newly diagnosed, untreated, AR+ve, TNBC invasive primary breast cancer. In this cohort, the trial evaluated the effects of preoperative therapy with enzalutamide alone.	

Primary: Geometric mean change in Ki67 expression in ER+ve Cohort

End point title	Geometric mean change in Ki67 expression in ER+ve Cohort[1]
End point description:	
Mean change in Ki67 expression is primary endpoint for the ER+ cohort only. The difference in geometric mean change (end of treatment – pre-treatment) in Ki67 expression between the two treatment groups (Mean ΔKi67). Geometric mean Ki67 suppression is calculated as 1 minus the back-transformation of the arithmetic mean of [ln(Ki67post) – ln(Ki67pre)].	
End point type	Primary
End point timeframe:	
Baseline to end of treatment	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comparison not applicable for single arm cohort

End point values	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	93		
Units: Ki67 expression				
geometric mean (confidence interval 95%)				
Geometric mean Ki67 suppression (%)	55.9 (47.1 to 63.2)	59.8 (53.1 to 65.6)		

Statistical analyses

Statistical analysis title	Relative Risk
Comparison groups	ER+ve Cohort Exemestane Only v ER+ve Cohort Enzalutamide and Exemestane

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.771
Method	t-test, 1-sided
Parameter estimate	Risk ratio (RR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.17

Primary: AR+ve TNBC individual anti-proliferative response

End point title	AR+ve TNBC individual anti-proliferative response[2][3]

End point description:

Individual anti-proliferative response rate (RRΔKi67), where response is defined as a ≥50% fall in Ki67 expression over the course of the study treatment.

End point type	Primary

End point timeframe:

Baseline to end of treatment

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Comparisons not applicable as single arm cohort

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comparisons not applicable as single arm cohort

End point values	AR+ve, TNBC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Response rate				
number (confidence interval 95%)				
RRΔKi67 response rate	4.8 (0.1 to 23.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean Ki67 expression at the end of study treatment

End point title	Geometric mean Ki67 expression at the end of study treatment

End point description:

ER+ve:
The difference in geometric mean Ki67 expression at the end of study treatment (Mean Ki67post) between the two treatment groups.

AR+ve:

Geometric mean Ki67 expression at the end of study treatment (Mean Ki67post).

End point type	Secondary

End point timeframe:

End of treatment

End point values	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	93	21	
Units: Ki67 expression				
geometric mean (confidence interval 95%)	5.9 (4.6 to 7.5)	5.7 (4.7 to 6.8)	19.8 (13.2 to 29.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Individual end-of treatment anti-proliferative response (RRKi67-Post)

End point title	Individual end-of treatment anti-proliferative response (RRKi67-Post)

End point description:

ER+ve:
Individual end of treatment anti-proliferative response rate (RRKi67-post) in both treatment groups, where response is defined as the natural logarithm of percentage positive Ki67 of less than 1 at the end of study treatment; the analysis will be limited to patients with pre-treatment ln(%Ki67)≥1.

AR+ve:
Individual end of treatment anti-proliferative response rate (RRKi67-post), where response is defined as the natural logarithm of percentage positive Ki67 of less than 1 at the end of study treatment; the analysis will be limited to patients with pre-treatment ln(%Ki67)≥1.

End point type	Secondary

End point timeframe:

End of treatment

End point values	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	48	93	21	
Units: Ki67 response rate				
number (confidence interval 95%)	14.6 (6.1 to 27.8)	21.5 (13.7 to 31.2)	0 (0 to 0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Individual anti-proliferative response (RRΔKi67) in ER+ve cohort

End point title	Individual anti-proliferative response (RRΔKi67) in ER+ve cohort[4]

End point description:

ER+ve:
Individual anti-proliferative response rate (RRΔKi67), where response is defined as a ≥50% fall in Ki67 expression over the course of the study treatment in both treatment groups.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comparison not applicable for single arm cohort

End point values	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	93		
Units: Anti proliferative response rate				
number (confidence interval 95%)				
anti-proliferative response (RRΔKi67)	54.2 (39.2 to 68.6)	63.4 (52.8 to 73.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean change in Caspase-3

End point title	Geometric mean change in Caspase-3

End point description:

ER+ve:
The difference in geometric mean change (end of treatment – pre-treatment) in Caspase-3 between the two treatment groups (Mean ΔCaspase-3).

AR+ve:
Geometric mean change in Caspase-3 at the end of study treatment (Mean ΔCaspase-3).

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	92	20	
Units: Caspase-3 expression				
geometric mean (confidence interval 95%)	1.7 (-102.4 to 52.2)	18.2 (-33.5 to 49.9)	0.1 (-34.6 to 25.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Individual apoptotic response (RRΔCaspase-3)

End point title	Individual apoptotic response (RRΔCaspase-3)

End point description:

ER+ve:
Individual apoptotic response rate (RRΔCaspase-3), where response is defined as a ≥50% increase in Caspase-3 over the course of the study treatment in both treatment groups.

AR+ve:
Individual apoptotic response rate (RRΔCaspase-3), where response is defined as a ≥50% increase in Caspase-3 over the course of the study treatment.

End point type	Secondary

End point timeframe:

Baseline to end of treatment

End point values	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	47	92	20	
Units: Response rate				
number (confidence interval 95%)	29.8 (17.3 to 44.9)	30.4 (21.3 to 40.9)	20 (5.7 to 43.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric mean change in Ki67 expression in AR+ve cohort

End point title	Geometric mean change in Ki67 expression in AR+ve cohort[5]

End point description:

The difference in geometric mean change (end of treatment – pre-treatment) in Ki67 expression between the two treatment groups (Mean ΔKi67). Geometric mean Ki67 suppression is calculated as 1 minus the back-transformation of the arithmetic mean of [ln(Ki67post) – ln(Ki67pre)].

End point type	Secondary

End point timeframe:

Baseline to end of treatment

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comparisons not applicable as single arm cohort

End point values	AR+ve, TNBC			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Ki67 expression				
geometric mean (confidence interval 95%)	7.5 (-8.2 to 21)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline until 30days after last day of treatment or study discontinuation/termination, whichever is later.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23

Reporting groups

Reporting group title	ER+ve Cohort Exemestane Only

Reporting group description:

Patients were given 25mg/day of exemestane for a minimum of 15 days and a maximum of 29 days until patients either had definitive surgery or primary medical treatment.

Reporting group title	ER+ve Cohort Enzalutamide and Exemestane

Reporting group description:

Patients were treated with enzalutamide plus exemestane for a minimum of 15 days and a maximum of 29 days before patients either had definitive surgery or primary medical treatment.

Reporting group title	AR+ve, TNBC

Reporting group description:

The AR+ve, TNBC cohort included patients with newly diagnosed, untreated, AR+ve, TNBC invasive primary breast cancer. In this cohort, the trial evaluated the effects of preoperative therapy with enzalutamide alone.

Serious adverse events	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 63 (3.17%)	1 / 129 (0.78%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events		0	0
Nervous system disorders			
Coma hypoglycemic			
subjects affected / exposed	1 / 63 (1.59%)	0 / 129 (0.00%)	0 / 27 (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			
Reduced general condition			
subjects affected / exposed	0 / 63 (0.00%)	1 / 129 (0.78%)	0 / 27 (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
Gastrointestinal disorders			

Gastritis			
subjects affected / exposed	1 / 63 (1.59%)	0 / 129 (0.00%)	0 / 27 (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

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

Non-serious adverse events	ER+ve Cohort Exemestane Only	ER+ve Cohort Enzalutamide and Exemestane	AR+ve, TNBC
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 63 (60.32%)	63 / 129 (48.84%)	15 / 27 (55.56%)
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 63 (12.70%)	19 / 129 (14.73%)	2 / 27 (7.41%)
occurrences (all)	8	20	2
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 63 (11.11%)	9 / 129 (6.98%)	2 / 27 (7.41%)
occurrences (all)	7	10	2
Dizziness			
subjects affected / exposed	6 / 63 (9.52%)	2 / 129 (1.55%)	3 / 27 (11.11%)
occurrences (all)	7	3	4
Vertigo			
subjects affected / exposed	4 / 63 (6.35%)	3 / 129 (2.33%)	1 / 27 (3.70%)
occurrences (all)	4	4	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 63 (6.35%)	19 / 129 (14.73%)	6 / 27 (22.22%)
occurrences (all)	4	22	6
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 63 (9.52%)	11 / 129 (8.53%)	3 / 27 (11.11%)
occurrences (all)	6	12	4
Diarrhoea			
subjects affected / exposed	2 / 63 (3.17%)	4 / 129 (3.10%)	2 / 27 (7.41%)
occurrences (all)	2	5	2
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	2 / 63 (3.17%)	1 / 129 (0.78%)	3 / 27 (11.11%)
occurrences (all)	2	1	3
Exanthema subitum			
subjects affected / exposed	0 / 63 (0.00%)	0 / 129 (0.00%)	2 / 27 (7.41%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
Mucositis			
subjects affected / exposed	0 / 63 (0.00%)	2 / 129 (1.55%)	2 / 27 (7.41%)
occurrences (all)	0	2	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 September 2015	This amendment related to the addition of two sites.
20 November 2015	This amendment related to the addition of one site.
08 January 2016	This amendment related to the change of PI at one site.
15 April 2016	This amendment related to the addition of new sites.
29 June 2016	This amendment related to the addition of new sites.
14 November 2019	This amendment was to extend the date of end of trial.

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.

The TNBC AR+ve cohort recruited 27/55 patients due to the funder not renewing stocks of existing IMP. The ER+ve cohort had completed recruitment, but the TNBC cohort was therefore stopped to recruitment early. The trial continued endpoint follow up.

Notes: