Clinical trial results:
A single group trial evaluating one cycle of adjuvant BEP chemotherapy in high risk, stage 1 non-seminomatous germ cell tumours of the testis (NSGCTT)

Summary

EudraCT number	2008-006295-29
Trial protocol	GB
Global end of trial date	11 September 2024

Results information

Result version number	v1 (current)
This version publication date	23 October 2025
First version publication date	23 October 2025

Trial information

Trial identification

Sponsor protocol code	ICR-CTSU/2008/10019

Additional study identifiers

ISRCTN number	ISRCTN37875250
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	The Institute of Cancer Research (ICR)
Sponsor organisation address	123 Old Brompton Road, London, United Kingdom,
Public contact	111 Trial manager, ICR - Clinical Trials and Statistics Unit, 111-icrctsu@icr.ac.uk
Scientific contact	111 Trial manager, ICR - Clinical Trials and Statistics Unit, 111-icrctsu@icr.ac.uk
Sponsor organisation name	University Hospital Birmingham NHS Trust
Sponsor organisation address	Queen Elizabeth Hospital Birmingham, Mindelsohn Way,Edgbaston, Birmingham, United Kingdom, B15 2GW
Public contact	111 Trial Manager, ICR-Clinical Trials and Statistics Unit, 111-icrctsu@icr.ac.uk
Scientific contact	111 Trial Manager, ICR-Clinical Trials and Statistics Unit, 111-icrctsu@icr.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	11 September 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show that one cycle of adjuvant BEP chemotherapy results in a 2 year recurrence rate of less than 5% in patients with high-risk stage 1 NSGCTT

Protection of trial subjects:

This trial adhered to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031). It was conducted in compliance with the protocol, the Data Protection Act (Z6364106) and other regulatory requirements as appropriate.
For trial entry, patients were given a verbal explanation, discussion and written information.
The Principal Investigator at each site was responsible for ensuring written informed consent was obtained for each patient.
Eligible patients were given as much time as they needed to consider and come to a decision about entering the trial, prior to giving consent for registration.
The patient information sheet, described fully which parties would have access to their identifiable personal information and patients were asked to
give consent to this.
The trial was overseen by an Independent Data Monitoring Committee, who reviewed the accumulating trial data and could recommend stopping the trial if there was any cause for concern about patient safety and if this were the case the patient's oncologist would be notified.
BEP(500) chemotherapy was prescribed by the investigator and dispensed from hospital pharmacy from their routine clinical supply for the duration of the trial. For bleomycin, etoposide and cisplatin, drug accountability, destruction and labelling guidelines are contained within the Trial Guidance Notes. All drugs will be labelled ‘for clinical trial use only’. Additional information on the safety and administration of these drugs can be found in their SmPC.
For infection prevention, all patients should be given prophylactic GCSF; either pegylated G-CSF 6mg subcut on day 4 or filgrastim daily sc according to local policy. All patients will be given prophylactic antibiotics; either levofloxacin 500mg po (recommended) on days 8 to 15 or ciprofloxacin 500 mg bd on days 8 to 15.
TheTrial Steering Committee (TSC) monitored and supervised the progress of the trial.

Background therapy:

Testicular cancer is the most common cancer in men aged 20-39. In 2003, 1855 cases were diagnosed in the UK.1 Approximately half of these were in men under 35. Non-seminoma germ cell tumours of the testis (NSGCTT) account for 40-45% of all testicular cancers and combined non-seminoma plus seminoma a further 15%. Approximately 60% of these present with stage 1 disease. Initial treatment for NSGCTT is radical surgery (orchidectomy) usually followed by adjuvant chemotherapy or surveillance.
If a single cycle of BEP(500) at the dose used in advanced disease, had a similar high rate of relapse-free survival (cure) to that seen with two lower dose cycles, this would reduce the overall burden of chemotherapy and healthcare resource usage and would be likely to lead to a change in practice globally.
A practice changing MRC study of two cycles of adjuvant BEP(360) reported an estimated recurrence rate of 2% but only rates >5% could be reliably excluded3. Evidence given below confirms the well known close relationship between long-term toxicity of chemotherapy and the total doses received. Consequently some centres have not adopted adjuvant chemotherapy preferring to offer intensive surveillance and, with a recurrence risk of 45%, thus expose almost half of their cases to at least three cycles of chemotherapy at relapse. During consultation, many such centres in the UK indicated that they would take part in the 111 trial employing just one cycle of chemotherapy if it was powered to exclude a

recurrence risk of >5% (as in the original study with two cycles). Evidence summarised above suggests that one cycle is very likely to be as effective as this, and will deliver just half the total doses of chemotherapy and thus less long-term toxicity

Evidence for comparator:

111 is a single group trial of a single cycle of adjuvant BEP(500) chemotherapy in high risk stage 1 NSGCTT. It aims to show a two year recurrence rate of less than 5%.

Actual start date of recruitment	18 March 2010
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: 246
Worldwide total number of subjects	246
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	5
Adults (18-64 years)	241
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between February 18, 2010 and March 31, 2014, 246 patients were registered from 33 UK NHS hospitals

Pre-assignment

Screening details:

Patients newly diagnosed with VI+ stage 1 NSCGCTT able to start chemotherapy (ideally 6wk-8weeks from orchidectomy.
Ten patients were replaced after they were identified as ineligible following registration because of raising tumour markers.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	BEP(500)

Arm description:

BEP(500) chemotherapy was given as follows: bleomycin 30,000 IU day 1, cisplatin 50 mg/m2 days 1 + 2, etoposide 165 mg/m2 days 1, 2 + 3 followed by bleomycin 30,000 IU days 8 + 15

Arm type	Experimental
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Regimen consists of bleomycin 30,000 IU day 1, bleomycin 30,000 IU days 8 + 15.
(1) Bleomycin may be given on either days 1 OR 2 depending on local hospital policy.
(2) Bleomycin may be given as 30 000IU iv infusion over 30 mins OR alternatively be given as 30 000IU im with 2 mls 1% lignocaine on days 8 and 15.
(3) Day 8 and 15 Bleomycin doses may be given +/- 24hours in the case of unavoidable delays e.g. public holidays, low platelets or neutrophils.

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Etoposide
165 mg/m2 iv infusion
Etoposide 165 mg/m2 days 1, 2 + 3

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Cisplatin
50 mg/m2 iv infusion
cisplatin 50 mg/m2 days 1 + 2

Number of subjects in period 1	BEP(500)
Started	246
Eligible and received treatment	236
Completed	236
Not completed	10
Ineligible	10

Baseline characteristics

Reporting groups	
Reporting group title	BEP(500)
Reporting group description:	
BEP(500) chemotherapy was given as follows: bleomycin 30,000 IU day 1, cisplatin 50 mg/m2 days 1 + 2, etoposide 165 mg/m2 days 1, 2 + 3 followed by bleomycin 30,000 IU days 8 + 15	

Reporting group values	BEP(500)	Total	
Number of subjects	246	246	
Age categorical Units: Subjects			
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	241	241	
From 65-84 years	0	0	
Age continuous Units: years			
median	30		
inter-quartile range (Q1-Q3)	25 to 39	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	246	246	
WHO performance status Units: Subjects			
Zero	230	230	
One	9	9	
Missing	7	7	
Tumour size Units: Subjects			
<2 cm	47	47	
2-5 cm	121	121	
>5 cm	71	71	
Missing	7	7	
Stage Units: Subjects			
pT2	237	237	
pT3	9	9	
Histology type Units: Subjects			
NSGCTT	132	132	
Mixed seminoma/NSGCTT	114	114	
Lymph nodes status Units: Subjects			
pN0	245	245	
pN1+	1	1	
Alpha-foetoprotein [AFP] at Baseline Units: Subjects			
Abnormal	16	16	

Normal	230	230	
Missing	0	0	
Alpha-foetoprotein [AFP] at Day 1 Units: Subjects			
Normal	2	2	
Abnormal	109	109	
Missing	135	135	
Human chorionic gonadotropin [HCG] at baseline Units: Subjects			
Normal	6	6	
Abnormal	240	240	
Missing	0	0	
Human chorionic gonadotropin [HCG] at Day 1 Units: Subjects			
Abnormal	6	6	
Normal	108	108	
Missing	132	132	
Lactate dehydrogenase (LDH) at baseline Units: Subjects			
Abnormal	32	32	
Normal	210	210	
Missing	4	4	
Lactate dehydrogenase (LDH) at Day 1 Units: Subjects			
Abnormal	14	14	
Normal	87	87	
Missing	145	145	

End points

End points reporting groups

Reporting group title	BEP(500)
Reporting group description:	
BEP(500) chemotherapy was given as follows: bleomycin 30,000 IU day 1, cisplatin 50 mg/m2 days 1 + 2, etoposide 165 mg/m2 days 1, 2 + 3 followed by bleomycin 30,000 IU days 8 + 15	
Subject analysis set title	Mock arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
test to report single arm trial	

Primary: Malignant recurrence rate at 2 years

End point title	Malignant recurrence rate at 2 years
End point description:	
The study is aiming to demonstrate that one cycle of adjuvant BEP (500) reduces the 2 year malignant recurrence rate to less than 5% in high-risk (vascular invasion positive) stage 1 NSGCTT. Malignant recurrence is defined as any of the following: • Progressive rise in tumour markers requiring treatment (AFP and/or HCG from 2 consecutive results taken a week apart that have shown at least a 50% increase above the ULN). • Development of metastases on clinical examination or imaging (CT scan and/or Chest X-ray). Disease related events were reviewed by at least 2 of the 111 recurrence reviewers who determined whether the event is a true recurrence. All disease related events were reviewed prospectively by the IDMC who confirmed whether the event counts as a primary endpoint malignant recurrence event.	
End point type	Primary
End point timeframe:	
2 years	

End point values	BEP(500)	Mock arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	236	236		
Units: Events				
Event - malignant recurrence	3	3		

Statistical analyses

Statistical analysis title	Exact binomial estimate - ITT population - 2 yrs
Statistical analysis description:	
The reported malignant recurrence rate at 2 years (and its 95% confidence interval) is estimated using exact probabilities in the subset of patients with complete 2-years fup (228)	
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Recurrence rate (%)
Point estimate	1.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	3.7

Notes:

[1] - Estimation

Statistical analysis title	KM estimate - ITT population - 2 yrs
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Recurrence rate (%)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	4

Notes:

[2] - In the absence of complete data at 2 years of follow-up, the recurrence rate and its 95% confidence interval is also estimated using Kaplan-Meier method. Patients with incomplete data at 2 years of follow-up were censored at the date when last seen prior to 2 years of follow-up. Patients with non malignant recurrence with teratoma differentiated (TD) in retroperitoneal nodes or any other suspected event with no evidence of malignancy were censored at the date when their event was reported

Statistical analysis title	Exact binomial estimate - PP population - 2 yrs

Statistical analysis description:

The reported malignant recurrence rate at 2 years (and its 95% confidence interval) is estimated using exact probabilities in the subset of patients with complete 2-years fup (207).

Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Recurrence rate (%)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	4.2

Notes:

[3] - Estimation

Statistical analysis title	KM estimate - PP population - 2 yrs

Statistical analysis description:

In the absence of complete data at 2 years of follow-up, the recurrence rate and its 95% confidence interval is also estimated using Kaplan-Meier method. Patients with incomplete data at 2 years of follow-up were censored at the date when last seen prior to 2 years of follow-up. Patients with non malignant recurrence with teratoma differentiated (TD) in retroperitoneal nodes or any other suspected event with no evidence of malignancy were censored at the date when their event was reported

Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Recurrence rate (%)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	4.4

Notes:

[4] - Estimation

Statistical analysis title	KM estimate - ITT population - 4 yrs
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Recurrence rate (%)
Point estimate	1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	4.6

Notes:

[5] - Estimation

Statistical analysis title	KM estimate - PP population - 4 years
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[6]
Parameter estimate	Recurrence rate (%)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	5.1

Notes:

[6] - Estimation

Secondary: Relapse Free Survival

End point title	Relapse Free Survival

End point description:

Relapse free survival was defined as time from registration until first confirmed relapse of testicular cancer or death from any cause. Patients alive with no event were censored at the date when they were last seen and patients with a secondary primary prior to their recurrence were censored at the time

point of the 2nd primary diagnosis.

End point type	Secondary

End point timeframe:

2 and 4 years

End point values	BEP(500)	Mock arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	236	236		
Units: Events	9	9		

Statistical analyses

Statistical analysis title	KM estimate - ITT population - 2 yrs

Statistical analysis description:

Kaplan-Meier method was used to estimate relapse free survival rate at 2 and 4 years along with the 95% confidence interval.

Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[7]
Parameter estimate	Proportion free of event (%)
Point estimate	97
Confidence interval	
level	95 %
sides	2-sided
lower limit	93.8
upper limit	98.6

Notes:

[7] - Estimation

Statistical analysis title	KM estimate - ITT population - 4 yrs

Statistical analysis description:

Kaplan-Meier method was used to estimate relapse free survival rate at 2 and 4 years along with the 95% confidence interval.

Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[8]
Parameter estimate	Proportion free of event (%)
Point estimate	96.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	92.6
upper limit	98

Notes:
[8] - Estimation

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival analysis included all deaths from any cause. Time was measured from registration and patients with no event were censored at the date when they were last seen.
There were three reported deaths; two occurred prior to and one after the 24 month follow up.

End point type	Secondary

End point timeframe:

2 and 4 years

End point values	BEP(500)	Mock arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	236	236		
Units: Events	3	3		

Statistical analyses

Statistical analysis title	KM estimate - ITT population - 2 yrs
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[9]
Parameter estimate	Proportion alive (%)
Point estimate	99.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	96.6
upper limit	99.8

Notes:
[9] - Estimation

Statistical analysis title	KM estimate - ITT population - 4 yrs
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[10]
Parameter estimate	Proportion alive (%)
Point estimate	98.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	95.7
upper limit	99.6

Notes:
[10] - Estimation

Secondary: Contralateral second primary testicular germ cell malignancy rate

End point title	Contralateral second primary testicular germ cell malignancy rate

End point description:

End point type	Secondary

End point timeframe:
2 years

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Teratoma differentiated recurrence rate

End point title	Teratoma differentiated recurrence rate

End point description:

End point type	Other pre-specified

End point timeframe:
2 and 4 years

End point values	BEP(500)	Mock arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	236	236		
Units: Events				
Recurrence event	3	3		

Statistical analyses

Statistical analysis title	KM ITT population - 2 year
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[11]
Parameter estimate	Recurrence rate (%)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	4

Notes:
[11] - Estimation

Statistical analysis title	KM ITT population - 4 year
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[12]
Parameter estimate	Recurrence rate (%)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	4

Notes:
[12] - Estimation

Other pre-specified: Recurrence Rate (any type)	
End point title	Recurrence Rate (any type)
End point description: Includes Malignant or Teratoma differentiated events	
End point type	Other pre-specified
End point timeframe: 2 and 4 years	

End point values	BEP(500)	Mock arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	236	236		
Units: Events	7	7		

Statistical analyses

Statistical analysis title	KM estimate - ITT population - 2 yrs
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[13]
Parameter estimate	Recurrence rate
Point estimate	2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	5.7

Notes:

[13] - Estimation

Statistical analysis title	KM estimate - ITT population - 4 yrs
Comparison groups	BEP(500) v Mock arm
Number of subjects included in analysis	472
Analysis specification	Pre-specified
Analysis type	other[14]
Parameter estimate	Recurrence rate
Point estimate	3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.5
upper limit	6.3

Notes:

[14] - Estimation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From registration to trial and within 30 days of the last administration of chemotherapy (3 weeks treatment + 30 days), which is not unequivocally due to progression of disease.

Adverse event reporting additional description:

Additionally, post-treatment delayed toxicities (not subject to expedited reporting) were described. AEs assessed by CTCAE v3 following BE500Px1, then every 2 mo until 6 mo, every 3 mo until 24 mo, every 4 mo during the third year, and every 6 mo during the fourth and fifth year.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3

Reporting groups

Reporting group title	On-treatment toxicity

Reporting group description: -

Reporting group title	Post-treatment delayed toxicity 2-12 months

Reporting group description:

An emergent toxicity over the 2 to 12 month period is defined as a toxicity not present at end of treatment or a toxicity event already present at end of cycle and that worsens since end of treatment.

Reporting group title	Post-treatment delayed toxicity 18-24 months

Reporting group description:

Toxicities collected at 18 and 24 months follow-up refer to seven pre-specified toxicity types and allows for four further toxicities to be reported at each visit.

Reporting group title	Post-treatment delayed toxicity 36-60 months

Reporting group description: -

Serious adverse events	On-treatment toxicity	Post-treatment delayed toxicity 2-12 months	Post-treatment delayed toxicity 18-24 months
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 236 (19.49%)	0 / 236 (0.00%)	0 / 215 (0.00%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Nervous system disorders			
Headache			

subjects affected / exposed	2 / 236 (0.85%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	2 / 236 (0.85%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	17 / 236 (7.20%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	17 / 17	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Neutropenia			
subjects affected / exposed	9 / 236 (3.81%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	9 / 9	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 236 (1.69%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	10 / 236 (4.24%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	10 / 10	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Constipation			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Diarrhoea			
subjects affected / exposed	3 / 236 (1.27%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Nausea			
subjects affected / exposed	3 / 236 (1.27%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	2 / 236 (0.85%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	4 / 236 (1.69%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	4 / 4	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	2 / 236 (0.85%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal inflammation			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Pleuritic pain			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 236 (0.85%)	0 / 236 (0.00%)	0 / 215 (0.00%)
occurrences causally related to treatment / all	2 / 2	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	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Myalgia			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Infections and infestations			
Anorectal cellulitis			

subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Sepsis			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 236 (0.42%)	0 / 236 (0.00%)	0 / 215 (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

Serious adverse events	Post-treatment delayed toxicity 36-60 months		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 207 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest pain				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Hypersensitivity				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Constipation				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Stomatitis				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	0 / 207 (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	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pharyngeal inflammation				
subjects affected / exposed	0 / 207 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pleuritic pain			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 207 (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 / 207 (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 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myalgia			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anorectal cellulitis			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed	0 / 207 (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	On-treatment toxicity	Post-treatment delayed toxicity 2-12 months	Post-treatment delayed toxicity 18-24 months
Total subjects affected by non-serious adverse events			
subjects affected / exposed	232 / 236 (98.31%)	91 / 236 (38.56%)	107 / 215 (49.77%)
Investigations			
Weight increased			
subjects affected / exposed	18 / 236 (7.63%)	33 / 236 (13.98%)	27 / 215 (12.56%)
occurrences (all)	18	33	27
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	69 / 236 (29.24%)	5 / 236 (2.12%)	3 / 215 (1.40%)
occurrences (all)	69	5	3
Lethargy			
subjects affected / exposed	135 / 236 (57.20%)	31 / 236 (13.14%)	34 / 215 (15.81%)
occurrences (all)	135	31	34
Neuropathy peripheral			
subjects affected / exposed	18 / 236 (7.63%)	21 / 236 (8.90%)	13 / 215 (6.05%)
occurrences (all)	18	21	13
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	78 / 236 (33.05%)	2 / 236 (0.85%)	5 / 215 (2.33%)
occurrences (all)	78	2	5
Leukopenia			
subjects affected / exposed	103 / 236 (43.64%)	1 / 236 (0.42%)	4 / 215 (1.86%)
occurrences (all)	103	1	4
Neutropenia			
subjects affected / exposed	96 / 236 (40.68%)	1 / 236 (0.42%)	5 / 215 (2.33%)
occurrences (all)	96	1	5
Thrombocytopenia			

subjects affected / exposed	142 / 236 (60.17%)	1 / 236 (0.42%)	7 / 215 (3.26%)
occurrences (all)	142	1	7
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 236 (7.20%)	1 / 236 (0.42%)	0 / 215 (0.00%)
occurrences (all)	17	1	0
Ear and labyrinth disorders			
Ototoxicity			
subjects affected / exposed	61 / 236 (25.85%)	13 / 236 (5.51%)	2 / 215 (0.93%)
occurrences (all)	61	13	2
Tinnitus			
subjects affected / exposed	0 / 236 (0.00%)	0 / 236 (0.00%)	16 / 215 (7.44%)
occurrences (all)	0	0	16
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	41 / 236 (17.37%)	2 / 236 (0.85%)	0 / 215 (0.00%)
occurrences (all)	41	2	0
Diarrhoea			
subjects affected / exposed	30 / 236 (12.71%)	13 / 236 (5.51%)	3 / 215 (1.40%)
occurrences (all)	30	13	3
Nausea			
subjects affected / exposed	66 / 236 (27.97%)	2 / 236 (0.85%)	0 / 215 (0.00%)
occurrences (all)	66	2	0
Stomatitits			
subjects affected / exposed	37 / 236 (15.68%)	1 / 236 (0.42%)	0 / 215 (0.00%)
occurrences (all)	37	1	0
Vomiting			
subjects affected / exposed	30 / 236 (12.71%)	1 / 236 (0.42%)	1 / 215 (0.47%)
occurrences (all)	30	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 236 (10.17%)	21 / 236 (8.90%)	12 / 215 (5.58%)
occurrences (all)	24	21	12
Dyspnoea			
subjects affected / exposed	27 / 236 (11.44%)	14 / 236 (5.93%)	10 / 215 (4.65%)
occurrences (all)	27	14	10

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	186 / 236 (78.81%)	14 / 236 (5.93%)	1 / 215 (0.47%)
occurrences (all)	186	14	1
Rash			
subjects affected / exposed	20 / 236 (8.47%)	5 / 236 (2.12%)	0 / 215 (0.00%)
occurrences (all)	20	5	0
Skin hyperpigmentation			
subjects affected / exposed	15 / 236 (6.36%)	7 / 236 (2.97%)	2 / 215 (0.93%)
occurrences (all)	15	7	2

Non-serious adverse events	Post-treatment delayed toxicity 36-60 months		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	98 / 207 (47.34%)		
Investigations			
Weight increased			
subjects affected / exposed	28 / 207 (13.53%)		
occurrences (all)	28		
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	31 / 207 (14.98%)		
occurrences (all)	31		
Neuropathy peripheral			
subjects affected / exposed	15 / 207 (7.25%)		
occurrences (all)	15		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 207 (2.42%)		
occurrences (all)	5		
Leukopenia			
subjects affected / exposed	5 / 207 (2.42%)		
occurrences (all)	5		
Neutropenia			

subjects affected / exposed	3 / 207 (1.45%)		
occurrences (all)	3		
Thrombocytopenia			
subjects affected / exposed	2 / 207 (0.97%)		
occurrences (all)	2		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences (all)	0		
Ear and labyrinth disorders			
Ototoxicity			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences (all)	0		
Tinnitus			
subjects affected / exposed	6 / 207 (2.90%)		
occurrences (all)	6		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	1 / 207 (0.48%)		
occurrences (all)	1		
Stomatitits			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 207 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 207 (3.86%)		
occurrences (all)	8		

Dyspnoea subjects affected / exposed occurrences (all)	10 / 207 (4.83%) 10		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	0 / 207 (0.00%) 0		
Rash subjects affected / exposed occurrences (all)	1 / 207 (0.48%) 1		
Skin hyperpigmentation subjects affected / exposed occurrences (all)	0 / 207 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 June 2012	Changes have been made to the protocol, patient information sheet (PIS) and consent form in order to reflect local practices, bring the advice given on fathering a child in line with the SmPCs and increase the patients' awareness of the sperm analysis which is conducted within the trial. The enclosed summary of proposed amendment document lists all of the amendments made to the protocol, PIS and consent form. A letter template which will be completed by centres and signed by the patient in order to request sperm analysis results is also enclosed. This new document has been written with the aim of increasing the quality of fertility data currently being reported to ICR-CTSU. The amendment also consists of the addition of two sites and the change of PI at two sites. There has also been an addition of a PIC which has been noted on the summary table for your information.
26 August 2014	This amendment is for an administrative change to the protocol whereby the definition of the end of study (section 14) has been amended to provide a single definition for the study end date.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31901440