Clinical trial results:
A randomised controlled phase III trial comparing hyperthermia plus mitomycin to a second course of bacillus Calmette-Guerin or standard therapy in patients with recurrence of non-muscle invasive bladder cancer following induction or maintenance bacillus Calmette-Guerin therapy.

Summary

EudraCT number	2008-005428-99
Trial protocol	GB
Global end of trial date	07 October 2016

Results information

Result version number	v1 (current)
This version publication date	01 December 2018
First version publication date	01 December 2018

Trial information

Trial identification

Sponsor protocol code	08/0365

Additional study identifiers

ISRCTN number	ISRCTN85785327
ClinicalTrials.gov id (NCT number)	NCT01094964
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint Research Office, 1st Floor Maple House, 149 Tottenham Court Road, London, United Kingdom, W1T 7DN
Public contact	HYMN Trial Office, Cancer Research Clinical Trial Unit University of Birmingham, UK, 44 121 414 6372, HYMN@trials.bham.ac.uk
Scientific contact	Professor John Kelly, University College London Medical School , 44 20 7679 6490, j.d.kelly@ucl.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	17 January 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim of the trial is to determine whether Hyperthermia plus the chemotherapy drug mitomycin is an effective therapy for patients with non-muscle invasive bladder cancer who have tumour recurrence following bacillus Calmette-Guerin (BCG) therapy. To do this we will be looking at disease-free survival in all patients; and the complete response rate after three months of treatment for those patients who entered the trial with Carcinoma In-Situ (a difference form of non-muscle invasive bladder cancer).

Protection of trial subjects:

The trial protocol instructed investigators on the treatment of patients, particular to follow the manufacturers' Summaries of Product Characteristics (SmPCs) for all drugs relevant to the trial (ie. mitomycin, BCG and that of the standard therapy specific to the site).

The protocol, and training of site staff on induction of the site into the trial, pointed out potential issues, such as patients experiencing intolerance to BCG during induction therapy and expected toxicities, which were listed in the protocol (Section 9.3 and appendix 8).

Mitomycin dose reductions were not permitted. Patients on BCG2 were treated on an intention-to-treat basis; any BCG dose reductions were at the discretion of the treating investigator. Treatment delays (potential reasons listed in protocol appendix 10) were permitted.

Background therapy:

All the drugs used as part of this trial were classed as Investigational Medicinal Products (IMPs) and were prescribed by the investigator and dispensed by the hospital pharmacy from their routine clinical supply, throughout the trial. All doses of Mitomycin and BCG were administered according to the protocol. All doses of the Institutional Standard therapies were administered per local practice.

Evidence for comparator:

Adjuvant intravesical BCG (bacillus of Calmette and Guérin) is an effective treatment for high risk non-muscle invasive bladder cancer (NMIBC)following transurethral resection (TUR) of papillary disease or as an ablative therapy for carcinoma in situ (CIS).

USA and European national guidelines advocate early cystectomy or re-challenge with BCG therapy following BCG failure, though accept its limited efficacy.[1-3] Although early radical cystectomy is the standard of care, there remains a 90-day mortality of between 3·0-6·9%.[4-5] There remains no accepted second line bladder sparing approach following BCG failure.

Although radical radiotherapy is not effective for NMIBC, the combination of intravesical mitomycin-C with radiofrequency-induced thermo-chemotherapy effect (RITE) is. Arends et al. compared RITE to intravesical BCG for intermediate and high risk BCG naïve NMIBC, reporting that recurrence free survival at 24 months supported earlier studies that reported RITE benefit for papillary NMIBC.[6]

This study represents the first randomised controlled multicentre trial comparing the use of adjuvant RITE with institutional standard of care NMIBC patients who have failed intravesical BCG treatment. The HYMN trial is to our knowledge the only RCT conducted in this setting.

Refs:
1. Han RF, et al. Urology 2006; 67(6): 1216-23
2. Sylvester RJ, et al. J Urol 2005; 174(1): 86-91
3. Babjuk M, et al. Eur Urol 2016 (Pub online: 17 Jun 2016)
4. Clark PE, et al. J Natl Compr Canc Netw 2016; 14(10): 1213-24

5.Tan WS, et al. Cancer Treat Rev 2016; 47: 22-31
6. Arends TJ, et al. Eur Urol 2016; 69(6): 1046-52

Actual start date of recruitment	06 May 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	10 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 104
Worldwide total number of subjects	104
EEA total number of subjects	104

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)	10
From 65 to 84 years	85
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

A total of 104 participants were recruited across 14 UK centres between 6 May 2010 and 15 July 2013, when the trial was terminated early.

Pre-assignment

Screening details:

Investigator identified potential patients from surveillance cystoscopy cases, surgery lists or multi-disciplinary team meetings, underwent full screening evaluation after being informed about the trial and giving informed consent. Consenting patients who met the entry criteria were randomised into the trial.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RITE

Arm description:

Hyperthermia plus mitomycin

Arm type	Experimental
Investigational medicinal product name	Mitomycin (with hyperthermia)
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

Baseline - treatment not given yet.

Arm title	Control

Arm description:

BCG or institutional standard therapy

Arm type	Institutional standard
Investigational medicinal product name	BCG immunotherapy
Investigational medicinal product code	PR2
Other name	BCG2
Pharmaceutical forms	Powder for bladder irrigation
Routes of administration	Intravesical use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	PR3
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Investigational medicinal product name	Interferon alfa-2b
Investigational medicinal product code	PR4
Other name	IFNα, alpha interferon, INTRON-A
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravesical use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Investigational medicinal product name	Mitomycin
Investigational medicinal product code	PR5
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravitreal use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Number of subjects in period 1	RITE	Control
Started	48	56
Completed	48	56

Period 2

Period 2 title	End of Trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	RITE

Arm description:

Mitomycin C plus hyperthermia (HM)

Patients received 6 weekly induction HM instillations using the Synergo® System, followed by a 6 week pause and cystoscopy assessment. If the patient was disease-free at assessment, they proceeded to maintenance HM, consisting of 6-weekly instillations of HM in year 1, then 8-weekly installations in year 2. Further treatment in those remaining disease-free at 24 months was at the clinician's discretion.

Each instillation was divided into 2x 30-minute cycles each with 20mg mitomycin dissolved in 50mls of sterile water. Bladder hyperthermia (42 +/-2°C) was delivered in combination with each instillation of mitomycin in accordance with the manufacturer’s operational guidelines. At the end of the treatment, the suspension was held in the bladder for as long as possible (max. 2 hrs).

Arm type	Experimental

Investigational medicinal product name	Mitomycin plus hyperthermia
Investigational medicinal product code	PR1
Other name	HM
Pharmaceutical forms	Powder for intravesical solution/solution for injection, Powder for solution for infusion
Routes of administration	Intravesical use

Dosage and administration details:

Two 30min instilation cycles of 20mg/50mls.

6 weekly instilations followed by 1 instilation every 6 weeks for thr first year and 1 instilation every 8 weeks for the second year.
Further treatment in diease free patients after 2 years is at the discretion of the treating clinician.

Arm title	Control

Arm description:

One of either:

1) Patients who failed previous induction BCG, ≤ 6 instillations : Second course of bacillus Calmette-Guerin therapy (BCG2) (Note : The small numnber of patients intollerant of BCG during induction therapy were randomised between HM and Intitutional Standard).

OR
2) For patients who failed previous maintenance BCG, had > 6 instillations or patients with BCG intolerance. Institutional Standard - best available standard therapy for BCG-failure, chosen at the discretion of the treating clinician on a case-by-case basis. This cohort was followed-up by surveillance visits, as per protocol.

Arm type	Active comparator
Investigational medicinal product name	BCG immunotherapy
Investigational medicinal product code	PR2
Other name	BCG2
Pharmaceutical forms	Powder for bladder irrigation
Routes of administration	Intravesical use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	PR3
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Investigational medicinal product name	Interferon alfa-2b
Investigational medicinal product code	PR4
Other name	IFNα, alpha interferon, INTRON-A
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Intravesical use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Investigational medicinal product name	Mitomycin
Investigational medicinal product code	PR5
Other name	
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravitreal use

Dosage and administration details:

As per Summary of Product Characteristics (SmPC) or local practice, whichever is applicable and defined at trial entry.

Number of subjects in period 2	RITE	Control
Started	48	56
Completed	48	56

Baseline characteristics

Reporting groups	
Reporting group title	RITE
Reporting group description: Hyperthermia plus mitomycin	
Reporting group title	Control
Reporting group description: BCG or institutional standard therapy	

Reporting group values	RITE	Control	Total
Number of subjects	48	56	104
Age categorical Units: Subjects			
Adults 18 years and over			0
Age continuous Units: years			
median	76.91	76.24	
inter-quartile range (Q1-Q3)	72.78 to 81.53	70.05 to 81.36	-
Gender categorical Units: Subjects			
Female	14	12	26
Male	34	44	78
Smoking Status Units: Subjects			
Never	28	33	61
Previous	4	2	6
Current	16	21	37
Not known	0	0	0
Tumour Stage Units: Subjects			
Tis + Ta	10	4	14
Tis + T1	2	6	8
Tis only	21	28	49
Ta only	11	10	21
T1 only	4	8	12
Not known	0	0	0
Tumour Grade Units: Subjects			
G1	0	1	1
G2	9	6	15
G3	18	21	39
Not known	21	28	49
Number of tumours identified Units: Subjects			
1 tumour	16	24	40
2 tumours	7	8	15
≥3 tumours	4	3	7

Not known	21	21	42
Previous BCG Units: Subjects			
Induction only (≤6 instillations)	18	19	37
Induction + maintenance (>6 instillations)	30	37	67
Institutional Standard			
Definitions: BCG - Bacillus Calmette-Guérin; MMC - Mitimycin C; EMDA - electromotive drug administration. Three participants did not receive their institutional standard treatment but were included in the intention to treat analysis.			
Units: Subjects			
BCG alone	0	14	14
MMC alone	0	9	9
EMDA MMC	0	13	13
Not given	0	20	20
N/A	48	0	48
Resection Units: Subjects			
Complete	28	33	61
Incomplete	4	2	6
Not known	16	21	37
Total Tumour Size Units: millimeter(s)			
median	5	5	
full range (min-max)	2 to 20	2 to 200	-

End points

End points reporting groups

Reporting group title	RITE
Reporting group description: Hyperthermia plus mitomycin	
Reporting group title	Control
Reporting group description: BCG or institutional standard therapy	
Reporting group title	RITE

Reporting group description:

Mitomycin C plus hyperthermia (HM)

Patients received 6 weekly induction HM instillations using the Synergo® System, followed by a 6 week pause and cystoscopy assessment. If the patient was disease-free at assessment, they proceeded to maintenance HM, consisting of 6-weekly instillations of HM in year 1, then 8-weekly installations in year 2. Further treatment in those remaining disease-free at 24 months was at the clinician's discretion.

Each instillation was divided into 2x 30-minute cycles each with 20mg mitomycin dissolved in 50mls of sterile water. Bladder hyperthermia (42 +/-2°C) was delivered in combination with each instillation of mitomycin in accordance with the manufacturer’s operational guidelines. At the end of the treatment, the suspension was held in the bladder for as long as possible (max. 2 hrs).

Reporting group title	Control

Reporting group description:

One of either:

1) Patients who failed previous induction BCG, ≤ 6 instillations : Second course of bacillus Calmette-Guerin therapy (BCG2) (Note : The small numnber of patients intollerant of BCG during induction therapy were randomised between HM and Intitutional Standard).

OR
2) For patients who failed previous maintenance BCG, had > 6 instillations or patients with BCG intolerance. Institutional Standard - best available standard therapy for BCG-failure, chosen at the discretion of the treating clinician on a case-by-case basis. This cohort was followed-up by surveillance visits, as per protocol.

Primary: Disease-free survival time

End point title	Disease-free survival time

End point description:

For patients without CIS at baseline and those with CIS at baseline but not at the 3-month surveillance visit - the disease-free survival interval was determined from the date of randomisation into the trial and the earliest of date of detection of recurrent disease, or date of death from any cause. For patients with CIS at baseline and at the 3-month surveillance visit - the interval was measured between the date of randomisation and the date of their 3-month surveillance visit. Disease recurrence was defined as histologically confirmed urothelial cell carcinoma or positive cytology.

Disease progression was defined as T2 disease (histologically confirmed) or evidence of extra-vesicular disease. In the absence of recurrent disease or death during the course of the trial, disease-free survival times will be censored at the last follow-up date. Patients who experience a distant upper-tract recurrence will be censored at the last available assessment.

End point type	Primary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	RITE	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	56		
Units: Months				
median (confidence interval 95%)	11.56 (7.35 to 18.91)	14.71 (6.17 to 31.12)		

Statistical analyses

Statistical analysis title	Disease free survival Log Rank Test

Statistical analysis description:

Experimental and control arms will be compared in terms of disease-free survival, recurrence-free survival, progression-free survival, overall survival and disease-specific survival times. Univariate time-to-event analyses will use the Kaplan-Meier method and the log-rank test.

Comparison groups	RITE v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.23
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	2.1

Primary: Complete response rate at 3 months

End point title	Complete response rate at 3 months

End point description:

For patients with CIS at randomisation, complete response at 3 months is defined as absence of visible tumour recurrence at cystoscopy, negative cytology and no evidence of CIS on random biopsy of the bladder.

End point type	Primary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	RITE	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	38		
Units: Patients				
number (not applicable)				
Complete Response	10	18		
Not Complete Response	23	20		

Statistical analyses

Statistical analysis title	Complete Response
Comparison groups	RITE v Control
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142
Method	Chi-squared

Secondary: Progression-free survival time

End point title	Progression-free survival time

End point description:

The progression-free survival interval was determined as the period between the date of entry into the trial and the earliest of either the date of detection of disease progression or date of death from any cause. Disease progression is defined as histologically confirmed stage T2 disease or greater following TUR (≥ pT2). For those patients who do not experience disease progression or who die during the course of the trial, progression-free survival times were censored at the last follow-up date. Patients who experience a distant upper-tract recurrence will be censored at the last available assessment.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	RITE	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[1]	56		
Units: number of patients analysed				
number (not applicable)	48	56		

Notes:

[1] - Units have been defined as number of patients analysed as median survival could not be calculated

Attachments (see zip file)	Progression Free survival/PFS.pdf

Statistical analyses

Statistical analysis title	Progression free survival Log Rank Test
Comparison groups	RITE v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	3.27

Secondary: Overall survival time

End point title	Overall survival time

End point description:

Overall survival was determined from the period between the date trial entry and the date of death from any cause. Patients who did not die during the course of the trial were censored at the last available assessment.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	RITE	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48[2]	56		
Units: number of patients analysed				
number (not applicable)	48	56		

Notes:

[2] - Units have been defined as number of patients analysed as median survival could not be calculated

Attachments (see zip file)	Overall Survival/OS.pdf

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	RITE v Control

Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	3.39

Secondary: Disease-specific survival time

End point title	Disease-specific survival time

End point description:

The disease-specific surviva interval was determined from the period between the date trial entry and the date of death due to bladder cancer. Patients who survived the course of the trial were censored at the last available assessment. Patients who died of other causes were censored at date of death due to other cause.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	RITE	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	56		
Units: Months				
number (not applicable)	48	56		

Statistical analyses

Statistical analysis title	Disease specific survival
Comparison groups	RITE v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	3.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	8.76

Secondary: Recurrence-free survival time

End point title	Recurrence-free survival time

End point description:

Recurrence-free survival was measured in patients with papillary disease only. It is defined in the same way as disease-free survival, with the important distinction that CIS at the first 3-month post-treatment visit was not included as an event, but instead a treatment failure which was censored. Patients who entered the trial with CIS and found to be CIS negative at the first surveillance visit, were also followed up for recurrence-free survival.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	RITE	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	56		
Units: Months				
median (confidence interval 95%)	12.67 (7.52 to 33.78)	13.07 (4.92 to 21.44)		

Statistical analyses

Statistical analysis title	Recurrence free survival
Comparison groups	RITE v Control
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.98
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.91

Secondary: Quality of Life

End point title	Quality of Life

End point description:

Quality of life was assessed at trial entry and every 3 months for the first year of treatment using the questionnaires EORTC QLQ-C30, BLS24 (a 24-item questionnaire for patients with superficial bladder cancer) and EQ5D.

End point type	Secondary

End point timeframe:

Outcome was assessed once all patients had completed a minimum of 12 months' follow-up from randomisation.

End point values	RITE	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: EQ5D				
arithmetic mean (standard deviation)	0.877 (± 0.139)	0.876 (± 0.154)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs and SAEs between trial entry until 30 days post final trial treatment and SAEs occurring after 30 days post last trial treatment considered treatment-related by the Investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4.0

Reporting groups

Reporting group title	RITE
Reporting group description: -	
Reporting group title	Control

Reporting group description: -

Serious adverse events	RITE	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 48 (16.67%)	3 / 56 (5.36%)	
number of deaths (all causes)	16	14	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fractured hip (neck of humerus)			
subjects affected / exposed	1 / 48 (2.08%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	2 / 48 (4.17%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 48 (2.08%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Death			
subjects affected / exposed	0 / 48 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 48 (2.08%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Increased urinary frequency			
subjects affected / exposed	1 / 48 (2.08%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney Injury			
subjects affected / exposed	0 / 48 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			
subjects affected / exposed	1 / 48 (2.08%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 48 (0.00%)	1 / 56 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 48 (2.08%)	0 / 56 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	RITE	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 48 (87.50%)	42 / 56 (75.00%)	
General disorders and administration site conditions			
Pain	Additional description: Pain/spasm		
subjects affected / exposed	28 / 48 (58.33%)	23 / 56 (41.07%)	
occurrences (all)	101	82	
Fever			
subjects affected / exposed	5 / 48 (10.42%)	13 / 56 (23.21%)	
occurrences (all)	6	30	
Fatigue			
subjects affected / exposed	15 / 48 (31.25%)	19 / 56 (33.93%)	
occurrences (all)	62	79	
Blood and lymphatic system disorders			
Myelosuppression			
subjects affected / exposed	2 / 48 (4.17%)	0 / 56 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Nausea			
subjects affected / exposed	4 / 48 (8.33%)	5 / 56 (8.93%)	
occurrences (all)	8	4	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 48 (4.17%)	2 / 56 (3.57%)	
occurrences (all)	4	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	7 / 48 (14.58%)	12 / 56 (21.43%)	
occurrences (all)	9	23	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	26 / 48 (54.17%)	30 / 56 (53.57%)	
occurrences (all)	90	106	
Increased urinary frequency			
subjects affected / exposed	26 / 48 (54.17%)	30 / 56 (53.57%)	
occurrences (all)	98	153	
Increased urinary urgency			

subjects affected / exposed	19 / 48 (39.58%)	27 / 56 (48.21%)	
occurrences (all)	85	101	
Incontinence			
subjects affected / exposed	10 / 48 (20.83%)	9 / 56 (16.07%)	
occurrences (all)	28	32	
Nocturia			
subjects affected / exposed	29 / 48 (60.42%)	30 / 56 (53.57%)	
occurrences (all)	90	106	
Haematuria			
subjects affected / exposed	23 / 48 (47.92%)	22 / 56 (39.29%)	
occurrences (all)	57	33	
Stricture			
subjects affected / exposed	3 / 48 (6.25%)	7 / 56 (12.50%)	
occurrences (all)	6	8	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 48 (27.08%)	13 / 56 (23.21%)	
occurrences (all)	21	15	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 August 2010	Version 2 Changes included • Eligibility exclusions changed to allow patients with stable hormonally controlled prostate cancer to enter the trial • Other Exclusion criteria clarified • Update the CTCAE from version 3 to version 4 thought out the protocol including appendix 9 and the supporting trial documents • Details of Photo dynamic detection (PDD) surveillance methods added • Device reporting responsibilities • Addition of contraception requirements • Update of contact details for trial coordinator due to a change in departmental name • Minor typographical and grammatical errors amended
26 November 2012	Version 3 Changes included • The Institutional Standard Therapy (control arm for patients who failed BCG maintenance) was changed from a pre-defined within site institutional standard, to the best standard of care chosen at the discretion of the treating clinician on a case-by-case basis. The protocol provides some examples of possible treatment options but the list is not all-inclusive. For these reasons, ATC codes have been used to cover the treatments that can be used (PR9). If the Standard Therapy chosen is not covered by the PIS appendices prepared, sites will use their own patient leaflet used in their routine local clinical practice. • In addition, active monitoring was added as an option for institutional standard therapy. • In response to the national BCG shortage we have added in the CTA the BCG-Medac brand with marketing authorisation outside the UK but within Europe Union (PR10). Because the BCG-Medac is available from several European countries, we cannot predict from which European country it will be ordered from. Therefore it is neither possible nor practical to include details of all the country specific Marketing Authorisation that may be used. For this reason we have completed section D2-1 of PR10 by leaving blank the Trade name, EV product code, which country granted the MA; under the MA number section we entered that "all intravesical BCG products have a marketing authorisation in a member state"; and finally, the question "Is this the Member State concerned with this application" could not be answered and "Not Answered" was ticked.
30 September 2013	Version 4 Amended to: • Include a central pathology review to collect tissue samples from pathology departments • Specify how CIS recurrences are confirmed locally: the presence of CIS will be determined locally by histology and by cytokeratin 20 (CK20) immunohistochemical staining following TUR • Add fluorescence in situ hybridisation (FISH) test for subsequent confirmation of CIS recurrences. FISH analysis will be performed by an independent laboratory on all CIS recurrences detected locally.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
19 July 2013	Early termination of recruitment. At a planned DMC meeting (2 Jul 2013) for the trial, the Chief Investigator and Trial Coordinator were advised that the DMC would be recommending to the TSC that recruitment of patients with CIS to the trial should be stopped. Because of the unusual nature of the recommendation, arrangements were made for the DMC to discuss their decision directly with the TSC. After their initial discussion, the trial management team received a communication from the TSC on the 17th July indicating closure of recruitment, and the necessity of re-examination of the data collected to date. On that basis recruitment was halted as a cautionary measure on the 19 Jul 2013. The TSC subsequently reviewed the interim analyses and, following discussion with the Chief Investigator, believed that further investigations and analyses were needed before any conclusions could be drawn or recommendations made to investigators. Part of the difficulty related to a concern that hyperthermia treatment may have lead to misinterpretation of the pathology. Following further discussions and a joint TSC/DMC meeting (6 Sep 2013), it was agreed that central pathology review for patients who failed to respond, or recurred on treatment, was crucially required. Central pathology review of the results plus an updated statistical analysis of the trial data were requested and reviewed after 3 months at a further joint TSC/DMC meeting when the decision was made to close the trial. In the intervening period, the TSC recommended that all trial patients remained on trial treatment. The TSC in consultation with the Chief Investigator wrote to the Principal Investigators, the Sponsor, the funding body (CTAAC) and Bladder Cancer CSG Chair on 25-Sep-2013.	-

Notes:

Limitations and caveats

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

Only 104 of the 242 subject target were recruited with 71 having CIS at baseline. Disease-free survival time analysis was underpowered but the CIS at baseline target was exceeded. There were insufficient data for cost effectiveness analysis.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30274699