



## 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<br>University of Birmingham, UK, 44 121 414 6372,<br>HYMN@trials.bham.ac.uk |
| Scientific contact           | Professor John Kelly, University College London Medical School<br>, 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:

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## 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:

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## 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:

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## 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:

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### 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  |
| <b>Arm title</b>             | 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.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | 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                             | IFN $\alpha$ , 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  |
| <b>Arm title</b>             | 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  $\pm$  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 instillation cycles of 20mg/50mls.

6 weekly instillations followed by 1 instillation every 6 weeks for the first year and 1 instillation every 8 weeks for the second year.

Further treatment in disease free patients after 2 years is at the discretion of the treating clinician.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Control |
|------------------|---------|

Arm description:

One of either:

1) Patients who failed previous induction BCG,  $\leq 6$  instillations : Second course of bacillus Calmette-Guerin therapy (BCG2) (Note : The small number of patients intolerant of BCG during induction therapy were randomised between HM and Institutional 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                             | IFN $\alpha$ , 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                 |

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Dosage and administration details:

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

| <b>Number of subjects in period 2</b> | RITE | Control |
|---------------------------------------|------|---------|
| Started                               | 48   | 56      |
| Completed                             | 48   | 56      |

## Baseline characteristics

### Reporting groups

|   |         |
|---|---------|
| Reporting group title   | RITE    |
| Reporting group description:<br>Hyperthermia plus mitomycin           |         |
| Reporting group title   | Control |
| Reporting group description:<br>BCG or institutional standard therapy |         |

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



|   |         |          |    |
|---|---------|----------|----|
| Not known   | 21      | 21       | 42 |
| Previous BCG<br>Units: Subjects   |         |          |    |
| Induction only ( $\leq 6$ 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<br>Units: Subjects  |         |          |    |
| Complete  | 28      | 33       | 61 |
| Incomplete  | 4       | 2        | 6  |
| Not known   | 16      | 21       | 37 |
| Total Tumour Size<br>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 number of patients intolerant of BCG during induction therapy were randomised between HM and Institutional 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

|   |                   |
|---|-------------------|
| <b>Statistical analysis title</b>       | 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 ( $\geq$ 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 <sup>[1]</sup> | 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

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Attachments (see zip file)</b> | Progression Free survival/PFS.pdf |
|-----------------------------------|-----------------------------------|

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | 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 <sup>[2]</sup> | 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

|                                   |                         |
|-----------------------------------|-------------------------|
| <b>Attachments (see zip file)</b> | Overall Survival/OS.pdf |
|-----------------------------------|-------------------------|

## Statistical analyses

|                                   |                  |
|-----------------------------------|------------------|
| <b>Statistical analysis title</b> | 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 survival 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

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | 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

|   |                          |
|---|--------------------------|
| <b>Statistical analysis title</b>       | 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                     |

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**Secondary: Quality of Life**

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|                 |                 |
|-----------------|-----------------|
| 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) |  |  |

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**Statistical analyses**

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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    | <p>Version 2<br/>Changes included</p> <ul style="list-style-type: none"><li>• Eligibility exclusions changed to allow patients with stable hormonally controlled prostate cancer to enter the trial</li><li>• Other Exclusion criteria clarified</li><li>• Update the CTCAE from version 3 to version 4 thought out the protocol including appendix 9 and the supporting trial documents</li><li>• Details of Photo dynamic detection (PDD) surveillance methods added</li><li>• Device reporting responsibilities</li><li>• Addition of contraception requirements</li><li>• Update of contact details for trial coordinator due to a change in departmental name</li><li>• Minor typographical and grammatical errors amended</li></ul>   |
| 26 November 2012  | <p>Version 3<br/>Changes included</p> <ul style="list-style-type: none"><li>• 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.</li><li>• In addition, active monitoring was added as an option for institutional standard therapy.</li><li>• 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.</li></ul> |
| 30 September 2013 | <p>Version 4<br/>Amended to:</p> <ul style="list-style-type: none"><li>• Include a central pathology review to collect tissue samples from pathology departments</li><li>• 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</li><li>• 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.</li></ul>  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption  | Restart date |
|--------------|---|--------------|
| 19 July 2013 | <p>Early termination of recruitment.</p> <p>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.</p> <p>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.</p> <p>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.</p> | -            |

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>