ISRCTN92816346 https://doi.org/10.1186/ISRCTN92816346

Is Gem-Doce an alternative to BCG treatment for people with early bladder cancer?

Submission date
22/07/2025

Recruitment status
Recruiting

Registration date
31/07/2025

Overall study status
Ongoing

Last Edited
31/07/2025

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The COBRA study is looking at a new treatment called Gem-Doce for people with early bladder cancer. The usual treatment, called BCG, has been used for over 40 years but often causes unpleasant side effects like bladder pain and flu-like symptoms. Many people don't finish the full course of BCG, and for some, the cancer still comes back or gets worse. The study aims to find out if Gem-Doce works just as well as BCG at stopping bladder cancer from returning, but with fewer side effects. It will also look at how the treatments affect people's quality of life and the cost of each option.

Who can participate?
Patients aged 18 years and over across the UK who have recently been diagnosed with early bladder cancer and would normally be treated with BCG may be invited to take part

What does the study involve?
People who join the study will be randomly given either BCG or Gem-Doce treatment. Both treatments are given directly into the bladder during hospital visits over 2 years. Everyone will have regular check-ups for five years, just like they would if they weren't in the study. Participants may also be asked to fill in optional questionnaires about their quality of life and healthcare use. These include questions about how they're feeling and how the treatment affects their daily life. There's also a short survey about background information, which is optional and confidential.

What are the possible benefits and risks of participating?
Taking part could help researchers find a better treatment for bladder cancer in the future. Gem-Doce may cause fewer side effects than BCG, but both treatments can still cause discomfort, such as pain when passing urine or flu-like symptoms. Severe side effects are rare, and all participants will be fully informed before deciding whether to take part.
People in the Gem-Doce group will have seven more treatment visits than those receiving BCG, but travel costs for these extra visits will be reimbursed.

Where is the study run from?
The Institute of Cancer Research (UK)

When is the study starting and how long is it expected to run for?
July 2025 to January 2032

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
cobra-icrctsu@icr.ac.uk

Plain English summary under review with external organisation

Study website
https://www.icr.ac.uk/cobra

Contact information

Type(s)
Public, Scientific

Contact name
Mr Steven Penegar

Contact details
The Institute of Cancer Research
15 Cotswold Road
Sutton
United Kingdom
SM2 5NG
+44 20 87224238
cobra-icrctsu@icr.ac.uk

Type(s)
Principal Investigator

Contact name
Prof Rakesh Heer

Contact details
Fulham Palace Road
London
United Kingdom
W6 8RF
-
cobra-icrctsu@icr.ac.uk

Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1008661

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 57987, ICR-CTSU/2024/10091

Study information

Scientific Title
Combination chemotherapy versus Bacillus Calmette-Guérin (BCG) for high-risk non-muscle invasive bladder cancer– a phase III multi-centre randomised controlled trial (COBRA)

Acronym
COBRA

Study objectives
The main objective of the COBRA trial is to investigate whether Gem-Doce treatment, put into the bladder, has similar treatment success rates to the standard treatment, BCG. We will assess whether it is similar at preventing disease returning, which has a high risk of progressing into more advanced cancer, which is life-threatening.

Secondary objectives:
1. To investigate whether Gem-Doce has similar rates as BCG in: any return or progression of bladder cancer after treatment, need for surgical removal of the bladder (cystectomy), death from cancer or any cause.
2. To compare side effects and the ability to complete a full course of each treatment
3. To investigate health-related quality of life as reported by participants.
4. To investigate the costs to the NHS and the cost-effectiveness of Gem-Doce treatment in comparison to BCG.

Ethics approval required
Ethics approval required

Ethics approval(s)
Not yet submitted, ref: 25/SC/0262

Study design
Interventional randomized parallel-group controlled trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
High-risk non-muscle invasive bladder cancer

Interventions
Patients will receive up to four treatments in different sequences. Randomisation process: Sequential randomisation by computer-generated random permuted blocks.

Treatment 1: BCG bladder instillations
Methodology: Intravesical BCG instillations
Generic drug name: Bacillus Calmette-Guérin
The dosage given: BCG (50 mg in 50 ml sodium chloride 0.9%)
Method of administration: Intravesical delivery
Frequency of administration: Six once-weekly induction intravesical instillations. Maintenance therapy delivered in three once-weekly instillations at months 3, 6, 12, 18 and 24 (15 instillations) until 24 months from the start of induction treatment
Total duration of treatment: 24 months

Treatment 2: Gem-Doce bladder instillations
Methodology: Sequential intravesical gemcitabine and docetaxel instillations
Generic drug name: Gemcitabine and docetaxel
The dosage given: Gemcitabine (1 g in 50 ml sodium chloride 0.9%) and Docetaxel (40 mg in 50 ml sodium chloride 0.9%)
Method of administration: Intravesical delivery
Frequency of administration: Six once-weekly induction intravesical instillations. Maintenance therapy delivered once-monthly from months 3 - 24 (22 instillations) until 24 months from the start of induction treatment
Total duration of treatment: 24 months

Follow-up: Clinical follow-up to 2 years post-treatment will inform the primary analysis. Thereafter, all participants will be followed up according to NICE guidelines.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Bacillus Calmette-Guérin, gemcitabine, docetaxel

Primary outcome measure
High-grade recurrence-free survival (hgRFS), i.e. time to first identification of high-grade recurrent disease, stage progression, metastatic disease or death from any cause. The primary

analysis of hgRFS is planned to take place once the target number of events has been observed, expected when participants have at least 2 years of follow-up and have completed study treatment.

Persistent/recurrent HG pT1 or HG Ta papillary bladder cancer following induction therapy or persistent carcinoma in situ at 6 months will be considered high-grade recurrence events. The development of nodal disease or distant metastatic disease (based on cross-sectional imaging or histological confirmation - where biopsy is done, histology results will supersede imaging) is considered a high-grade recurrence event.

Secondary outcome measures

1. Recurrence-free survival, defined in whole days as the time from the date of randomisation to the date of confirmed recurrence of non-muscle invasive bladder cancer (includes all events described in the primary endpoint, as well as recurrences of any grade); analysis after approximately 2 years follow-up (at the time of the primary endpoint).
2. Progression-free survival, defined in whole days as the time from the date of randomisation to the date of confirmed progression to muscle-invasive bladder cancer, nodal disease, distant metastatic disease, or death from any cause; analysis after approximately 2 years of follow-up (at the time of the primary endpoint)
3. Cystectomy-free survival, defined in whole days as the time from the date of randomisation to the date of cystectomy; analysis after approximately 2 years of follow-up (at the time of the primary endpoint)
4. Cancer-specific survival, defined in whole days as the time from the date of randomisation to the date of death specifically from bladder cancer; analysis after approximately 2 years of follow-up (at the time of the primary endpoint)
5. Overall survival, defined in whole days as the time from the date of randomisation to the date of death; for those who have not been reported as dead at the time of analysis; analysis after approximately 2 years of follow-up (at the time of the primary endpoint)
6. Complete response rate at 6 months (in patients with carcinoma in situ at baseline only), measured as the number of patients with an absence of cancer at 6-month cystoscopy (in patients with carcinoma in situ at baseline only)
7. Number of instillations received, measured over the 24-month induction and maintenance visit schedule of allocated treatment
8. Clinician assessed adverse events, measured by clinician-reported symptoms using CTCAE v5 over the 24-month induction and maintenance visit schedule
9. Patient-reported outcomes: health-related quality of life with an emphasis on overall quality of life, physical functioning, urinary symptoms and intravesical treatment issues, measured over the 24-month maintenance visit follow-up period, measured by the generic EORTC QLQ-F17, disease-specific QLQ-NMIBC24 and the generic EQ-5D-5L validated instruments
10. Costs to the NHS and personal social services, measured over the 24-month maintenance visit follow-up period and extrapolated over the patient lifetime
11. Incremental cost per quality-adjusted life year gained, measured over the 24-month maintenance visit follow-up period and extrapolated over the patient lifetime from responses to the EQ-5D-5L, cross-walked from responses to the EORTC QLQ-F17 as a sensitivity analysis

Unless advised otherwise by the IDMC, secondary endpoints will be reported at the time of the primary analysis.

Overall study start date

21/07/2025

Completion date
31/01/2032

Eligibility

Key inclusion criteria
1. Written informed consent prior to any study-specific procedures
2. Age >=18 years
3. WHO performance status 0-3
4. A new diagnosis of high-risk urothelial NMIBC with no variant histology:
4.1. pT1 G2-3/high grade tumour (with or without CIS) OR
4.2. pTa G3/high grade tumours (with or without CIS) OR
4.3. Isolated carcinoma in situ (CIS)
5. Complete papillary tumour removal (apart from residual CIS) via TURBT
6. All patients with pT1 at initial TURBT should have had re-TURBT if there was no muscle in initial TURBT specimens. Re-resection should also be considered for patients with HG Ta if no muscle was present or for patients with HG T1 with muscle present at initial TURBT, according to local practice
7. Willing to use an effective method of contraception
8. Willing and able to comply with the follow-up schedule

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
520

Key exclusion criteria
1. Any previous history of urothelial cancer
2. History of pure non-urothelial cell bladder cancer (adenocarcinoma, squamous cell carcinoma)
3. Evidence of neuroendocrine (small/ large cell) sarcomatoid, micropapillary or plasmacytoid variant urothelial cell cancer
4. Any urethral involvement
5. Any medical condition that contraindicates study treatment, including any known allergy to gemcitabine, docetaxel or BCG
6. Known pregnancy and/or currently breastfeeding
7. Known HIV, Hepatitis B or C with detectable viral load within 30 days prior to randomisation
8. Ongoing immunosuppressive medication, including steroids (>10 mg/day) - people receiving short courses (two weeks maximum) of steroids due to be discontinued prior to randomisation or using inhaled and topical steroids are eligible for randomisation
9. Active or treated malignancy within 1 year of randomisation (not including non-melanomatous

skin carcinoma, NICE low-risk prostate cancer (T1/T2a, Gleason 6 PSA <10), in situ carcinoma of any site)

Date of first enrolment
01/08/2025

Date of final enrolment
31/07/2029

Locations

Countries of recruitment
United Kingdom

Study participating centre
Not provided at time of registration
United Kingdom
-

Sponsor information

Organisation
Institute of Cancer Research

Sponsor details
15 Cotswold Road
Sutton
England
United Kingdom
SM2 5NG
+44 (0)20 87224238
cobra-icrctsu@icr.ac.uk

Sponsor type
University/education

Website
http://www.icr.ac.uk/

ROR
https://ror.org/043jzw605

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Peer-reviewed scientific journals
Internal report
Conference presentation
Publication on website
Submission to regulatory authorities

The ICR-CTSU supports the wider dissemination of information from the research it conducts and increased cooperation between investigators. Formal requests for data sharing will be considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines.

Requests are via a standard proforma describing the nature of the proposed research and the extent of data requirements. Data recipients are required to sign a data release form which describes the conditions for release and requirements for data transfer, storage, archiving, publication and Intellectual Property.

Data sharing will be in accordance with the ICR Policy on Sharing Personal Data which is in line with the requirements of the United Kingdom's General Data Protection Regulations (UK GDPR). Data are not normally shared until the primary trial results have been published so as not to compromise the principal research question. Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymising identifiable patient data. Additionally, all indirect identifiers that may lead to deductive disclosures will be removed in line with Cancer Research UK's Data Sharing Guidelines. All participants will be required to provide written consent to participate in the clinical trial, at which point optional consent for future data sharing will also be sought.

Requests for data will be reviewed by the Trial Management Group (TMG) in terms of scientific merit and ethical considerations, including patient consent. Data sharing will be undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the independent Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC).

Intention to publish date
31/01/2033

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from cobra-icrctsu@icr.ac.uk

IPD sharing plan summary
Available on request