# A Phase 3, Randomized, Active-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of EN3348 (MCC) as Compared with Mitomycin C in the Intravesical Treatment of Subjects with BCG Recurrent or Refractory Non-Muscle Invasive Bladder Cancer

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| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Renal and urinary tract neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON35360

**Source**
ToetsingOnline

**Brief title**
EN3348-303

### Condition

- Renal and urinary tract neoplasms malignant and unspecified

**Synonym**
Bladder Cancer/Urothelial carcinoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Endo Pharmaceuticals Inc.
**Source(s) of monetary or material Support:** Commercial Sponsor

## Intervention

**Keyword:** Non-muscle invasive bladder cancer

## Outcome measures

### Primary outcome

* Event-free survival - the interval from randomization to an event

* Safety - will include all adverse events (AEs) including serious adverse

events (SAEs), vital signs, physical exams and laboratory test results

### Secondary outcome

* Event-free survival rate at 1 and 2 years

* Recurrence rate at 1 and 2 years

* Progression rate at 1 and 2 years * number of subjects progressing to muscle

invasive disease (T2 or higher)

* Time to cystectomy * interval from randomization to cystectomy

* Overall survival

# Study description

### Background summary

Bladder cancer is the most common malignant tumor in the urinary tract,

accounting for over 3.3% of all cancers. An estimated 357,000 new bladder cancer cases occurred worldwide in 2002 and approximately 145,000 deaths, with population-based 5-year survival rates ranging from 40% to 80%. Bladder cancer is relatively common in developed countries, where 63% of all incident cases occur.
Urothelial (also known as transitional cell) carcinoma is by far the most common histological subtype, accounting for more than 90% of all bladder cancers. Urothelial carcinoma (UC) can be subdivided into subtypes according to their invasiveness (ie, non-muscle invasive or muscle invasive) or shape (ie, papillary or flat). The majority of UC (70%-75%) present as non-muscle invasive bladder cancers (NMIBC)
A transurethral resection of a bladder tumor (TURBT) is the standard initial treatment for non-muscle invasive bladder cancer of all visible lesions. The TURBT also confirms the diagnosis and allows pathologic examination of the resected tumor specimen for stage and grade. However, most of these tumors (60% to 70%) have a tendency to recur after TURBT and some (15% to 25%) are at high risk for progression to muscle invasion. As a result, adjuvant intravesical instillations with chemotherapeutic or immunotherapeutic agents have been used in conjunction with TURBT and have shown to reduce tumor recurrences.
Although intravesical chemotherapeutic agents have been shown to reduce tumor recurrences, none of these agents has proven to be of benefit in preventing disease progression. Bacillus Calmette-Guérin (BCG), an immunotherapeutic agent, has shown to prolong the time to development of muscle invasion.
Despite a high initial complete response rate with BCG, a significant number of subjects will eventually fail BCG therapy and notable toxicities are observed with continued, prolonged use of BCG. In fact, BCG failures of 30% and 33% have been reported for CIS and high grade T1 tumors, respectively. Guidelines from the American Urological Association (AUA), National Comprehensive Cancer Network (NCCN), and the European Association of Urology (EAU) have recommended cystectomy for patients who have recurrent or persistent disease.
These efficacy and toxicity considerations have led to the search for more effective and safer therapeutic agents for non-muscle invasive bladder cancer. Mycobacterial cell wall-DNA complex (MCC), prepared from Mycobacterium phlei (M. phlei) is one such agent.

**Study objective**

The primary objective of this study is to evaluate the efficacy of EN3348 as compared with mitomycin C in the treatment of subjects with BCG recurrent or refractory NMIBC.

The secondary objective is to evaluate the safety of EN3348 as compared with mitomycin C in the treatment of subjects with BCG recurrent or refractory NMIBC.

**Study design**

This is a phase 3, randomized, active-controlled, open-label, multicenter study designed to evaluate the efficacy and safety of EN3348 in subjects with BCG recurrent or refractory NMIBC (Ta high grade, T1, carcinoma in situ [CIS]). The randomization will be 1:1 and stratified by geographical region (North America, India, Europe), tumor pathology (CIS versus no CIS), prior BCG response (refractory versus recurrent), and prior intravesical (IVe) chemotherapy (yes/no) using minimization technique.

Duration of Treatment: Subjects will receive study treatment with either EN3348 or mitomycin C for up to 12 months. This study consists of 4 phases:
Screening Phase (-8 Weeks): Subjects will be qualified for study entry by review of inclusion and exclusion criteria during the Screening Phase, which will last up to 8 weeks.
Induction Phase (6 Weeks): Subjects will receive weekly instillations of either EN3348 or mitomycin C for total of 6 doses.
Maintenance Phase (10 Months): Subjects will receive monthly instillations of study drug for up to an additional 10 doses (up to Month 12). In addition, subjects will undergo disease assessments every 3 months, with a mandatory biopsy required at Month 6.
Subjects will have completed the Maintenance Phase after completing the Month 12 instillation.
Follow-Up Phase (Up to Approximately 24 Months):
All randomized subjects, regardless of number of study drug instillations received, will be followed until the End of Study. For an individual subject, the end of study can be achieved by completing all required assessments through the termination of the trial or earlier due to early discontinuation or withdrawal of informed consent.
Assessments will be conducted every 3 months for months 13 through 24 and every 6 months from Month 25 through Month 36/End of Study.

## Intervention

Subjects will receive weekly instillations of either EN3348 or mitomycin C for total of 6 doses during induction phase and monthly instillations of study drug for up to an additional 10 doses (up to Month 12) during maintanace phase.

## Study burden and risks

In addition to the side effects which are possible as a result of study drugs administration, patients may experience discomforts or risks associated with such study procedures as cystoscopy, bladder biopsy/TURBT, urinary catheterization, anesthesia, blood drawing.

Considering the dual mechanisms of action and clinical activity of EN3348 in the BCG refractory and recurrent settings and its safety advantage of containing no live mycobacteria, it may offer a treatment option for patients

whose disease is refractory or recurrent after BCG.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

Subjects are eligible for inclusion into the study if the following criteria are met:
1. Males and females who are 18 years of age or older at time of consent signing
2. Have either BCG recurrent or refractory NMIBC:
a. Refractory disease is defined as evidence of persistent high grade bladder cancer (TaHG, T1, and/or CIS) at least 6 months from the start of a full induction course of BCG with or without maintenance/re-treatment at 3 months
b. Recurrent disease is defined as reappearance of disease after achieving a tumor-free status by 6 months following a full induction course of BCG with or without maintenance/re-treatment at 3 months. Subjects with recurrent disease must have recurred within 18 months

following the last dose of BCG
A full induction course of BCG is defined as at least 5 out of 6 total expected instillations of BCG within a period of 2 months, regardless of dose strength.
3. Have histologically confirmed NMIBC (according to 2004 WHO classification) within 8 weeks prior to randomization:
a. High grade Ta papillary lesion(s)
b. High or low grade T1 papillary lesion(s) (biopsy sample must include evidence of muscularis propria)
c. CIS, with or without Ta or T1 papillary tumor(s) of any grade
4. Have had all visible papillary and resectable CIS lesion(s) removed by TURBT within 8 weeks prior to randomization
5. Available for the duration of the study including follow-up (approximately 36 months)
6. Have an Eastern Cooperative Oncology Group (ECOG) performance status grade of 2 or less
7. Have no evidence of urothelial carcinoma involving the upper urinary tract or the urethra (confirmed by extravesical work up, which may include radiological imaging and/or biopsy) within 6 months prior to randomization:
a. If previous work up occurred more than 6 months prior to randomization, extravesical work up must be repeated prior to randomization in order to determine eligibility
8. Subjects (male and female) of child-bearing potential (including female subjects who are post-menopausal for less than 1 year) must be willing to practice effective contraception (as defined by the Investigator) while on treatment and be willing and able to continue contraception for 30 days after their last dose of study treatment
9. Is able to understand and give written informed consent

## Exclusion criteria

Subjects meeting the following criteria will be excluded from participation in the study:
1. Current or previous history of muscle invasive bladder tumors
2. Current or previous history of positive lymph nodes and/or metastatic bladder cancer
3. Current evidence of pure squamous cell carcinoma, pure adenocarcinoma or pure undifferentiated carcinoma of the bladder
4. Currently receiving systemic anti-cancer therapy (cytotoxic/cytostatic or immunotherapy)
5. Currently receiving treatment with a prohibited therapy (refer to section 10.2.1, Prohibited Medications)
6. Current or prior history of systemic lupus erythematosus
7. Systemic immunotherapy within 6 months of randomization (refer to section 10.2.1, Prohibited Medications)
8. Treatment with an investigational agent within 30 days or 5 half-lives from randomization, whichever is longer
9. Prior treatment with an intravesical chemotherapeutic agent within 3 months of randomization, with the exception of a single perioperative dose of chemotherapy immediately post-TURBT (not considered treatment)
10. Prior treatment with EN3348 (MCC) or any other mycobacterial cell wall composition or formulation

11. Refractory to mitomycin C (failure to achieve tumor-free status following minimum of a 6-week induction course of mitomycin C) at any time in the subject*s disease history
12. Contraindication to mitomycin C
13. Untreated urinary tract or bladder infection
14. ANC <1000/*L and hemoglobin <10 g/dL
15. Known cardiovascular disease such as myocardial infarction within the past 3 months, unstable angina pectoris, congestive heart failure (New York Heart Association [NYHA] Class III or IV) or uncontrolled cardiac arrhythmia
16. Female subjects who are pregnant or lactating
17. Congenital or acquired immune deficiency
18. Have current or history of documented or suspected malignancy of any organ system (diagnosed, treated or untreated) within the past 5 years (with the exception of localized transitional cell carcinoma of the ureter treated with ureterectomy or nephroureterectomy, adequately treated basal cell or squamous cell carcinoma of the skin or asymptomatic non-metastatic prostate cancer either previously successfully treated or currently under active surveillance or receiving hormone therapy only)
19. Bladder contracture or history of an inability to retain the instillate for a minimum of 1 hour, even with premedication
20. Inability to tolerate intravesical administration or intravesical surgical manipulation (cystoscopy or biopsy)
21. Clinically significant active infections
22. Any medical or psychiatric condition which, in the opinion of the Investigator, would preclude the participant from adhering to the protocol or completing the trial per protocol

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Will not start |
| Start date (anticipated): | 08-02-2012 |

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| Enrollment: | 4 |
| Type: | Anticipated |

### Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | EN3348/MCC - Mycobacterial cell wall-DNA complex (MCC) |
| Generic name: | MCC |
| Product type: | Medicine |
| Brand name: | Mitomycin C |
| Generic name: | Mitomycin C |
| Registration: | Yes - NL intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 22-12-2011 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |
| Approved WMO Date: | 20-06-2012 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
| --- | --- |
| EudraCT | EUCTR2011-003496-11-NL |
| ClinicalTrials.gov | NCT01200992 |
| CCMO | NL38103.091.11 |