A total of 140 patients who meet study entry criteria will be enrolled and treated. The first 35 patients enrolled and treated must have CIS (with or without papillary disease). After these 35 patients are treated and 10 complete responders are documented, the enrollment will expand to also allow patients with papillary disease only who meet inclusion and exclusion criteria. It is estimate that a total of approximately 70 to 100 patients with CIS will be treated.

All enrolled patients will enter the 10-week induction phase and begin treatment with BC-819. Treatment should begin within 7 days of enrollment and ≤42 days from the last TUR or biopsy. During the induction phase, patients will receive an intravesical instillation of BC-819 at a dose of 20 mg/50 mL aqueous solution once per week for 10 weeks according to the induction phase treatment schedule (see Table 12.1).

Upon completion of the induction phase, patients will continue with maintenance therapy of BC-819 every 3 weeks beginning at Week 12 (Visit 11) and continuing for the next 84 additional weeks until the end of the study, defined as completion of the 96-week visit (Visit 39).

During the study, patients will undergo repeat direct visualization (ie, cystoscopy ± biopsy and cytology) and repeat TUR (as needed for cause) every 12 weeks during the first and second year. Patients with persistent CIS which does not resolve by the 12-week assessment, or at subsequent 12-week assessments, or who have recurrence or new evidence of CIS or high-grade papillary disease at any time will be discontinued and classified as nonresponders and recurrences in the primary and secondary endpoint analyses. Patients benefiting from treatment, with no documented high-grade recurrence or progression, will continue to receive maintenance therapy every 3 weeks. Appearance or persistence of lower grade tumors will not be considered as recurrence for the primary and secondary endpoint analyses, and patients with only low-grade tumors should continue treatment after resection and histological confirmation.

**NUMBER OF PATIENTS (PLANNED):** It is planned to enroll and treat 140 patients (N=140), of which 70 to 100 are estimated to have CIS (with or without papillary disease). Assuming at least 70 patients with CIS, this sample size will provide over 95% power to detect a difference between CR rate in CIS patients of 20% and an alternative hypothesis proportion of 40% using an exact binomial test with a nominal 0.05 two-sided significance level. If 100 CIS patients are enrolled, the power will be approximately 92% to detect a difference from 20% assuming an alternative hypothesis proportion of 35%. The power is higher to detect a difference from CR rates lower than 20%.

# 14. DATA QUALITY

## 14.1 Source Data and Records

Source data/records contain all the information that is necessary for the reconstruction and evaluation of the study. Source data/records are 1) original records; 2) certified copies of original records; 3) observations; 4) laboratory reports; and 5) data sheets, whether recorded in hard copy or electronic medical records. Source data/records are to be kept within the control of the investigator until the end of the regulatory retention period. The investigator will permit study-related monitoring, audit(s), IRB review(s) and regulatory inspection(s), with direct access to all the required source records.

## 14.2 Electronic Data Capture

Clinical study data will be transcribed from source records by the investigator or a designee into a validated, 21 Code of Federal Regulations Part 11 compliant, Internet-based electronic data capture (EDC) system. Data entry into the EDC system should be completed in a timely manner following completion of each patient visit.

The investigator and staff will be trained to use the EDC system before enrollment of the first patient. A list of the status of each user, including an audit trail of status changes, will be maintained.

At the end of the study, the completed online eCRF must be reviewed and signed electronically by the investigator named in the study protocol or by a designated sub-investigator authorized to sign. A certification must be obtained from all authorized persons to sign electronically, indicating that their electronic signature is equivalent to their hand-written signature. In order to sign electronically, the signer must log in with his/her username and password and re-enter his/her password on the page(s) requiring a signature(s).

## 14.3 Data Management

A Data Management Plan will be created to specifically identify how data management will be performed for the study.

Queries will be handled within the EDC application. The monitors and data managers (DMs) will be the only persons who can generate a query. Under direction of the investigator, the site coordinator will address the query. If the query is because of a data entry error, the coordinator can immediately make the corrections in the applicable eCRF pages. If the query needs clarification, the coordinator will contact the investigator for resolution. The coordinator will then enter the correct value or submit an answer to the query without modifying the data. The assigned data management staff and/or monitor will then review the corrected eCRF pages and/or answer. If the data are changed correctly or the answer is acceptable, data management or monitor will close the query. If the answer is not acceptable, the monitor will submit an additional query for clarification. All changes to the database require a “Reason for Change” and are subject to an audit trail. The audit trails identify the changed data, reason(s) for change, who changed the data and the time, and date of the change.

Centralized monitoring will be performed at an agreed-upon frequency, as defined in the Clinical Monitoring Plan. Meetings with the clinical research and DM teams are held to review and

| | |
|---|---|
| MedDRA | Medical Dictionary for Regulatory Activities |
| NMIBC | non-muscle invasive bladder cancer |
| PEI | polyethylenimine |
| PFS | progression-free survival |
| PT | preferred term |
| QLQ-NMIBC24 | Non-Muscle Invasive Bladder Cancer Questionnaire |
| re-TUR | repeat transurethral resection |
| SAE | serious adverse event |
| SOC | system organ class |
| SOP | standard operating procedure |
| SUSAR | serious unexpected suspected adverse reaction |
| TEAE | treatment-emergent adverse event |
| TUR | transurethral resection |
| US | United States |
| WBC | white blood cell |
| WHO | World Health Organization |

# 9. INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan—Description

This study, BC-819-18-204 (referred to as Study 204), is a Phase 2, open-label, monotherapy, single-arm, multicenter clinical trial of BC-819 (inodiftagene vixteplasmid) in patients with NMIBC adequately treated with BCG whose disease is BCG-unresponsive according to the FDA guidance (FDA 2018). Patients with BCG-unresponsive disease have NMIBC that is unlikely to benefit from and should not be treated with further intravesical BCG.

Patients are to have recurred or progressed after adequate treatment, had BCG-unresponsive disease, had a TUR, and then had all papillary disease completely resected and obvious CIS disease fulgurated when indicated. Patients with T1 disease should undergo resection of the base of the lesion when possible (biopsy should contain muscle fiber). Patients must have 1 or more of the following: completely resected high-grade T1 disease, CIS disease, or completely resected high-grade Ta disease. There is no intravesical or medical standard of care for this patient population, and the usual course is radical cystectomy.

A total of 140 patients who meet study entry criteria will be enrolled and treated during the approximately 15-month enrollment period. The first 35 patients enrolled and treated must have CIS (with or without papillary disease). After these 35 patients are treated and 10 complete responders are documented, the enrollment will expand to also allow patients with papillary disease only who meet inclusion and exclusion criteria. It is estimate that a total of approximately 70 to 100 patients with CIS will be treated.

All enrolled patients will enter the 10-week induction phase and begin treatment with BC-819. Treatment should begin within 7 days of enrollment and ≤42 days from the last TUR or biopsy. During the induction phase, patients will receive an intravesical instillation of BC-819 at a dose of 20 mg/50 mL aqueous solution once per week for 10 weeks according to the induction phase treatment schedule (see Table 12.1).

Upon completion of the induction phase, patients will continue with maintenance therapy of BC-819 every 3 weeks beginning at Week 12 (Visit 11) and continuing for the next 84 additional weeks until the end of the study, defined as completion of the 96-week visit (Visit 39).

During the study, patients will undergo repeat direct visualization (ie, cystoscopy ± biopsy and cytology) and re-TUR (as needed for cause) every 12 weeks during the first and second year. Patients with persistent CIS which does not resolve by the 12-week assessment, or at subsequent 12-week assessments, or who have recurrence or new evidence of CIS or high-grade papillary disease at any time will be discontinued and classified as nonresponders and recurrences in the primary and secondary endpoint analyses. Patients benefiting from treatment, with no documented high-grade recurrence or progression, will continue to receive maintenance therapy every three weeks. Appearance or persistence of lower grade tumors will not be considered as recurrence for the primary and secondary endpoint analyses, and patients with only low-grade tumors should continue treatment after resection and histological confirmation.

## 9.2 Discussion of Study Design and Choice of Control Group(s)

The presentations and discussion at a workshop held at the annual AUA meeting in May 2013 serve as the rationale for this study. A summary of that meeting was published by Jarow et al.

(2014). The FDA recently published a more detailed guidance document in February 2018 that reiterates the challenges for drug development in this specific population, clearly stating that there is currently no effective therapy for patients with high-grade NMIBC unresponsive to BCG other than cystectomy (FDA 2018). Therefore, a single-arm Phase 2 clinical study is acceptable.

## 9.3 Selection of Study Population

Eligible patients must be BCG-unresponsive, adequately treated, who after recurrence have had all papillary disease resected and CIS fulgurated when indicated.

### 9.3.1 Inclusion Criteria

Eligible patients must meet the following inclusion criteria:

1. Male or female patients ≥18 years of age at the time of consent
2. Patient must have been adequately treated with BCG defined as at least one of the following (FDA 2018):
    a. At least five of six doses of an initial induction course plus at least two of three doses of maintenance therapy
    b. At least five of six doses of an initial induction course plus at least two of six doses of a second induction course
    c. A single course of induction BCG can qualify if the patient has T1 high-grade disease at first evaluation (see 3c)
3. Patient must be BCG-unresponsive according to the FDA guidance defined as at least one of the following (FDA 2018):
    a. Persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy. An assessment within 15 months can also qualify when no assessment was done 12 months after completion of adequate BCG therapy.
    b. Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy. An assessment within 9 months can also qualify when no assessment was done 6 months after completion of adequate BCG therapy.
    c. T1 high-grade disease at the first evaluation following a single course of induction BCG qualifies (Lerner et al. 2015, Steinberg et al. 2016)
4. Patient must have, at study entry, NMIBC indicated by 1 or more of the following:
    a. Ta or T1 high-grade disease
        i. No more than 42 days may elapse between the start of protocol therapy and complete resection of Ta/T1 papillary disease qualifying the patient for the study
    b. CIS disease
        i. Obvious areas of CIS should be fulgurated prior to start of therapy when indicated
5. Patient must have no known evidence of concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra within 6 months of enrollment
6. Patient must have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2

- Changes in quality of life over time, as measured by the EORTC QLQ-C30 (a general questionnaire for cancer) and the QLQ-NMIBC24 (a specific questionnaire for NMIBC disease)

Additionally, patients with appearance of new high-grade disease (ie, new high-grade papillary disease in patients with CIS only or new CIS in patients with papillary disease only) will be classified as treatment failures in EFS analyses, as will patients with CIS at baseline whose CIS lesions have not resolved by the 12-week cystoscopy, or who have recurrent CIS at later cystoscopies.

At each follow-up visit, response of existing lesions and presence of any new lesions will be evaluated (by direct visualization and biopsies as needed) and reported in the eCRF. Recurrences must be proven and documented by biopsy.

A biopsy will be performed at screening and when indicated by direct visualization at other visits for purposes of staging and grading.

The laboratory results from pathology specimens (samples taken from re-TUR of tumors) will be reviewed by the study investigator. These laboratory results will be provided to the investigator from the certified and/or accredited laboratory local to the site, where the samples were processed. If there is no certified and/or accredited laboratory on site, the specimen may be shipped to another agreed upon certified and/or accredited laboratory for analysis and reporting of results to the study investigator. There is no central laboratory review and/or evaluation requirement in this study. For these efficacy analyses, recurrence will be considered biopsy proven and/or sufficiently documented following a local investigative pathology review that deems the specimen as positive.

In the case where a patient consistently has positive cystoscopy or cytology results (3 or more) but repeated negative biopsy, the patient will **not be** considered a treatment failure for the EFS analyses.

## 11.3 Safety Variables

The safety endpoint is occurrence of AEs according to CTCAE version 5.0, regardless of relationship to study medication.

### 11.3.1 Clinical Laboratory

Standard clinical chemistry, hematology, and urinalysis assessments will be conducted periodically during the study at the hospital facilities. Abnormalities that develop after the start of study medication and abnormalities present at baseline, but which worsen by at least 1 CTCAE grade on study will be considered AEs when clinically significant. Investigator discretion is allowed in determination of AEs, and investigators will assess grade, severity, and causality of any abnormalities considered AEs.

### 11.3.2 Adverse Events

#### *11.3.2.1 Adverse Events and Serious Adverse Events*

An AE is any untoward medical occurrence in a subject participating in a clinical trial. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the

use of the study medication, whether or not considered related to the study medication. AEs will be collected from the time a patient signs the ICF until 30 days after the final visit. AEs occurring prior to the start of treatment will be recorded in the eCRF and shown in listings but not in tables of AEs. Only TEAEs (ie, those AEs that begin or worsen in severity after the start of treatment) will be tabulated in the AE tables and discussed in the clinical study report.

Pre-existing, known clinically significant conditions observed at screening should be recorded as medical history. Worsening of a pre-existing condition by at least 1 grade per CTCAE version 5.0 should be recorded as an AE.

The definition of AEs also includes accidental injuries, reasons for any change in medication (drug and/or dose) other than planned titration, reasons for admission to a hospital, or reasons for surgical procedures (unless for minor elective surgery for a pre-existing condition). It also includes AEs commonly observed and AEs anticipated based on the pharmacological effect of the study medication. All new laboratory abnormalities and baseline abnormalities worsening by at least 1 CTCAE grade must be recorded as an AE when clinically significant.

A TEAE is any AE occurring after start of study medication or pre-existing medical condition that worsens in intensity after start of study medication.

AEs should be recorded as diagnoses, if available. If not available, separate sign(s) and symptom(s) are recorded. One diagnosis/symptom should be entered per record.

Note that death is not an event; however, the cause of death is. An exception is the event of sudden death of unknown cause. Note that hospitalization is not an event; however, the reason for hospitalization is. Procedures are not events; however, the reasons for conducting the procedures are. In general, only the reason for conducting the procedure will be captured as an AE. If deemed necessary by the investigator, a procedure can be captured along with the reason for conducting the procedure.

An overdose or medication error is not an AE unless it is temporally associated with an unfavorable or unintended sign or symptom.

Each AE is to be classified by the investigator as serious or non-serious. An SAE is any untoward medical occurrence or effect that occurs at any dose which:

- Results in death
- Is life-threatening (ie, an immediate risk of death)
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is associated with a congenital anomaly/birth defect
- Is an important medical event

| Category | Definition |
|---|---|
| Definitely | This category applies when, after careful medical consideration, there is almost no consideration of other causation. |
| Probably | There is a clinically plausible time sequence between onset of the AE and study treatment administration. The AE is unlikely to be caused by a concurrent and/or underlying illness, other drugs, or procedures. If applicable the AE follows a clinically consistent resolution patter upon withdrawal of study drug. |
| Possibly | There is a clinically plausible time sequence between onset of the AE and study treatment administration, but the AE could also have been caused by the concurrent/underlying illness, other drugs, or procedures. "Possible" should be used when study treatment administration is one of several biologically plausible causes of the AE. |
| Unlikely | The AE is most likely due to a non-study-treatment-related cause. However, association with the study treatment cannot be completely ruled out. |
| Not related | Another cause of the AE is most plausible, and a clinically plausible temporal sequence is inconsistent with the onset of the AE and study treatment administration and/or a causal relationship is considered biologically implausible. |

AEs with the causality assessed as unlikely and not related are categorized as not related to study medication for regulatory reporting. Investigators will assess events for relationship to study medication (BC-819) and independently to study procedures (eg, catheterization for direct visualization or administration of medicine). Investigators may assess an event as possibly related to more than 1 cause.

**All SAEs must be reported immediately (no more than 24 hours after becoming aware of the event).** The investigator must complete the initial SAE Report Form and fax/e-mail it within 24 hours according to the SAE Report Form instructions. Any SAES occurring within 30 days following study discontinuation must also be reported. The sponsor medical monitor or delegate is responsible for providing the sponsor's assessment of causality and expectedness that will be

**Table 13.1 Urinary Tract–Related Adverse Events**

| System Organ Class | Preferred Term |
|---|---|
| Infections and infestations | Urinary tract infection |
| | Urosepsis |
| Investigations | Blood creatinine increased |
| Renal and urinary disorders | Any |

Written narratives will be provided for all serious, unexpected or other significant AEs that are judged to be of special interest because of their clinical importance.

### 13.6.2 Clinical Laboratory

Clinical laboratory results will be summarized with descriptive statistics at baseline, each study time point, and with shifts from baseline for key variables. Units of measurement for laboratory results will be centrally converted, when necessary, to a uniform standard for presentation of results across all participating study sites (eg, via the eCRF software). Particular attention will be paid to urinary findings.

Laboratory abnormalities that develop after the start of study medication and abnormalities present at baseline, but which worsen by at least 1 CTCAE grade on study will be considered AEs when clinically significant. Investigator discretion is allowed in determination of AEs, and investigators will assess grade, severity, and causality of any abnormalities considered AEs.

instructions. Monitors will verify that sites have an adequate supply for ongoing and new patients.

During the course of the study, the monitor is responsible for the accountability and reconciliation of the IMP. To assist with this, the following documents will need to be reviewed by the monitor, as appropriate:

- IMP Shipment Request Form
- IMP Receipt
- The monitor will return the IMP as instructed by the sponsor at the completion of the study at the site. The monitor will need to do the following:
    - Complete IMP Return Forms (if any)
    - Record all return shipping information

### 14.10 Laboratory Samples and Analysis

The laboratory samples will be collected and analyzed at a laboratory that is local to the site.

Monitors will review local laboratory documentation to ensure that the relevant laboratory certifications and/or accreditations are current. Additionally, monitors will verify that the local laboratory maintains accurate and adequate records of laboratory sample storage, temperature logs, and periodic laboratory equipment calibration events.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION AND EXCLUSION:**

Eligible patients must meet the following inclusion criteria:

1. Male or female patients ≥18 years of age at the time of consent
2. Patient must have been adequately treated with BCG defined as at least one of the following (FDA 2018):
    a. At least five of six doses of an initial induction course plus at least two of three doses of maintenance therapy
    b. At least five of six doses of an initial induction course plus at least two of six doses of a second induction course
    c. A single course of induction BCG can qualify if the patient has T1 high-grade disease at first evaluation (see 3c)
3. Patient must be BCG-unresponsive defined as at least one of the following (FDA 2018):
    a. Persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of completion of adequate BCG therapy. An assessment within 15 months can also qualify when no assessment was done 12 months after completion of adequate BCG therapy
    b. Recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy. An assessment within 9 months can also qualify when no assessment was done 6 months after completion of adequate BCG therapy
    c. T1 high-grade disease at the first evaluation following a single course of induction BCG qualifies (Lerner et al. 2015, Steinberg et al. 2016)
4. Patient must have, at study entry, NMIBC indicated by 1 or more of the following:
    a. Ta or T1 high-grade disease
        i. No more than 42 days may elapse between the start of protocol therapy and complete resection of Ta/T1 papillary disease qualifying the patient for the study
    b. CIS disease
        i. Obvious areas of CIS should be fulgurated prior to start of therapy when indicated
5. Patient must have no known evidence of concomitant upper tract urothelial carcinoma or urothelial carcinoma within the prostatic urethra within 6 months of enrollment
6. Patient must have an Eastern Cooperative Oncology Group performance status ≤2
7. Patient must have adequate hematologic function, as demonstrated by the following:
    a. Hemoglobin level ≥10 g/dL
    b. Absolute neutrophil count ≥1.5 x $10^9$/L
    c. Platelet count ≥100 x $10^9$/L
8. Patient must have adequate liver and renal function as demonstrated by the following:
    a. Aspartate aminotransferase and alanine aminotransferase each ≤3.0 x upper limit of normal
    b. Total bilirubin ≤1.5 x upper limit of normal, unless prior documentation of Gilbert's syndrome in which case, 3.0 mg/dL is allowed
    c. Serum creatinine ≤1.5 x upper limit of normal or measured or calculated creatinine clearance ≥30 mL/min
9. Female patients of childbearing potential must use maximally effective birth control during the period of therapy (ie, a combination of 2 regulatory approved methods), must be willing to use contraception for 1 month after the last study drug infusion, and must have a negative urine or serum pregnancy test result upon entry into the study. Otherwise, female patients must be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile

discuss data quality and data management issues and minutes of meetings maintained. When necessary, the Clinical Monitoring Plan will be revised and corrective actions implemented.

### 14.4 Study Master File

The Study Master File for both the investigator and the sponsor will be maintained in either hard copy or electronically using 21 Code of Federal Regulations Part 11 compliant software.

### 14.5 Record Retention

All study records will be retained for a period of time as defined by the regulatory authority for the country in which the investigation is conducted. Generally, this means at least 2 years after the date on which the drug is approved by the regulatory authority for marketing for the indication studied in the clinical trial. In other situations (eg, where the investigation is not in support of or as part of an application for a research or marketing permit), a period of 2 years after the date on which the entire clinical program is completed, terminated or discontinued, or the investigational application under which the investigation is being conducted is terminated or withdrawn by the regulatory authorities.

In the event the investigator retires, relocates, or for any other reason withdraws from the responsibility for maintaining records for the period of time required, custody of the records may be transferred to any other person who will accept responsibility for the records. Notice of such a transfer must be given in writing to the sponsor. The investigator must contact the sponsor before disposal of any records related to this study.

### 14.6 Confidentiality of Patient Data

The investigator will ensure that the confidentiality of the patients' data will be preserved. In the eCRF or any other documents submitted to the sponsor, the patients will not be identified by their names, but by a unique identifier number in the study. The investigator will maintain documents not meant for submission to the sponsor (eg, the confidential patient identification code and the signed ICFs) in strict confidence. All data are subject to monitoring, audits, and inspection.

### 14.7 Monitoring Plan

The Clinical Monitoring Plan identifies the monitoring schedule and the rationale for the frequency and type of monitoring visits. A detailed Clinical Monitoring Plan will be developed by the sponsor and the identified contract research organization.

### 14.8 Site Visits

Sites will undergo qualification, initiation, monitoring, and close-out visits per INC Research standard operating procedure (SOP).

### 14.9 Investigational Medicinal Product

Monitors will verify that the investigator maintains accurate and adequate records, including dates of treatment, duration of treatment, and appropriate follow-up, and that the source documents are being maintained. Monitors will perform IMP accountability and verify storage conditions of the IMP (secure location, temperature logs, etc) in accordance with manufacturers'

## 5. GLOSSARY OF TERMS

**Screened patient**: Patient first identified as being possibly eligible for the study. Standard of care diagnostic, laboratory tests, and clinical assessment may be part of the data set used to determine patient eligibility.

**Eligible patient:** A patient meeting inclusion/exclusion criteria and eligible to be treated.

**Screen failure**: A patient who signed the informed consent form but was found to be ineligible to receive study drug.

**Treated patient:** Any patient who was administered study drug.

7. Patient must have adequate hematologic function, as demonstrated by the following:
    a. Hemoglobin level ≥10 g/dL
    b. Absolute neutrophil count ≥1.5 x $10^9$/L
    c. Platelet count ≥100 x $10^9$/L
8. Patient must have adequate liver and renal function as demonstrated by the following:
    a. Aspartate aminotransferase and alanine aminotransferase each ≤3.0 x upper limit of normal
    b. Total bilirubin ≤1.5 x upper limit of normal, unless prior documentation of Gilbert's syndrome in which case, 3.0 mg/dL is allowed
    c. Serum creatinine ≤1.5 x upper limit of normal or measured or calculated creatinine clearance ≥30 mL/min
9. Female patients of childbearing potential must use maximally effective birth control during the period of therapy (ie, a combination of 2 regulatory approved methods), must be willing to use contraception for 1 month after the last study drug infusion, and must have a negative urine or serum pregnancy test result upon entry into the study. Otherwise, female patients must be postmenopausal (no menstrual period for a minimum of 12 months) or surgically sterile
10. Male patients who are sexually active must be willing to use a double-barrier contraceptive method upon study enrollment, during the course of the study, and for 1 month after the last study drug infusion
11. Patient must be able to understand and sign an ICF
12. Patient must be able to comply with protocol requirements, including attendance at required clinic visits

### 9.3.2 Exclusion Criteria

The presence of any of the following excludes a patient from study enrollment:

1. Patient has current or previous evidence of muscle invasive (muscularis propria) or metastatic bladder cancer disease
2. Patient has received prior investigational therapy for NMIBC
3. Patient has received any therapy for NMIBC within 10 weeks before the start of study treatment other than surgical resection, 1 dose of chemotherapy, and previous BCG
4. Patient is intolerant to previous BCG treatment in the absence of meeting other criteria for BCG unresponsiveness and adequate BCG therapy
5. Patient has received external beam radiation therapy for bladder cancer at any time or for any other condition
6. Patient has an active infection, including urinary tract infection (viral, bacterial, or fungal) and cystitis
7. Patient has urinary tract signs or symptoms that preclude retention of drug in the bladder; this does not include anticholinergic drugs
8. Patient is known to have tested positive for human immunodeficiency virus (HIV). No HIV testing is required if patient is not known have tested positive

An AE caused by an overdose or medication error is considered serious if a criterion listed in the definition above is fulfilled.

Important AEs that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject's safety or may require medical or surgical intervention to prevent one of the outcomes listed above.

SAEs also include any other event that the investigator or sponsor judges to be serious or which is defined as serious by the regulatory agency.

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient using concise medical terminology. In addition, each study patient will be questioned about AEs. The question asked will be "Since you began taking the study medication, have you had any health problems?"

#### *11.3.2.2 Procedures for Assessing, Recording, and Reporting Adverse Events and Serious Adverse Events*

Throughout the study, the investigator will closely monitor each patient for evidence of drug intolerance and for the development of clinical or laboratory evidence of AEs. All AEs (expected or unexpected) which occur during the course of the study, whether observed by the investigator or by the patient, and whether or not thought to be drug-related, will be reported and followed until resolution or until they become stable.

The description of the AE will include description of event, start date, stop date, intensity, if it was serious, relationship to test drug, change in test drug dosage, if the patient died, and if treatment was required.

AEs will be graded according to CTCAE version 5.0. A copy of the terminology can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

For AEs not included in the CTCAE version 5.0, the following criteria will apply:

| Grade | Description |
|---|---|
| 1 | Mild |
| 2 | Moderate |
| 3 | Severe |
| 4 | Life-threatening or disabling |
| 5 | Fatal |

AEs will be coded, grouped, and tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) according to body system organ class (SOC). Events will be coded into 1 of the following 5 causality categories:

considered when determining if the event qualifies as a serious unexpected suspected adverse reaction (SUSAR) requiring expedited reporting to regulatory authorities.

Sponsor Medical Monitor: Dr. Frank Haluska
E-mail: frank.haluska@anchiano.com

**Table 11.1 Contact Research Organization Contact Information**

| **SAE Reporting Fax Number and Email Address** | |
|---|---|
| Fax Number | +1 877 464 7787 |
| Email Address | INCDrugsafety@INCResearch.com |

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor and designated clinical research organizations maintain a quality assurance system with written SOPs to ensure that clinical trials are conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and applicable regulatory requirements.

## 15.1 Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Sponsor Quality Assurance or its designees or to regulatory authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents. These audits or inspections may take place at any time during or after the study and are based on the national regulations as well as International Council for Harmonisation guidelines.

## 15.2 Laboratory Quality Standards

Laboratory tests or evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the SOPs of the central laboratories.