CLINICAL STUDY PROTOCOL

Protocol Title: A Phase 2 Study of BC-819 in Patients with Non-Muscle Invasive Bladder Cancer Whose Disease is Unresponsive to Bacillus Calmette-Guerin

Protocol Number:	**BC-819-18-204 (version 1.4)**
Study Product:	BC-819 (inodiftagene vixteplasmid)
Indication:	Non-muscle invasive bladder cancer in patients whose disease is unresponsive to bacillus Calmette-Guerin
Phase:	2
EudraCT Number:	2017-000655-67
IND Number:	13588
Study Institutions/Locations:	Multicenter, multinational study
Name and Address of Sponsor:	Anchiano Therapeutics Israel Ltd 1/3 High Tech Village Givat Ram, Jerusalem, Israel PO Box 39264 913902, Israel
Good Clinical Practice (GCP) Statement:	This study will be performed in compliance with GCP, including the archiving of essential documents.

DOCUMENT APPROVAL

This study will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

SPONSOR REPRESENTATIVES:

_____ _____

Signature: Date

Print Name: _____

Title: _____

_____ _____

Signature: Date

Print Name: _____

Title: _____

1. SYNOPSIS

TITLE: A Phase 2 Study of BC-819 in Patients with Non-Muscle Invasive Bladder Cancer Whose Disease is Unresponsive to Bacillus Calmette-Guerin

INVESTIGATIONAL PRODUCT: Recombinant DNA plasmid complexed with polyethylenimine, hereafter referred to as BC-819 or inodiftagene vixteplasmid.

INDICATION: Non-muscle invasive bladder cancer (NMIBC) in patients whose disease is unresponsive to bacillus Calmette-Guerin (BCG)

PHASE OF DEVELOPMENT: 2

INVESTIGATIONAL SITES/LOCATIONS: Multicenter, multinational (United States [US] and Non-US sites)

OBJECTIVES:

Primary:

The primary objective is to determine, for the patients with baseline CIS:

- The proportion that achieves a complete response after treatment with inodiftagene vixteplasmid

Secondary:

The secondary objectives are to determine the:

- Proportion of patients with absence of high-grade recurrent or persistent disease at 48 weeks (overall population and subgroup of patients with CIS)
- Proportion of patients with absence of high-grade recurrent or persistent disease at 12, 24, 36, 72, and 96 weeks (overall population and subgroup of patients with CIS)
- Time to recurrence (Kaplan-Meier plot)
- Proportion of patients who are progression-free at 48, 72, and 96 weeks
- Overall survival of patients enrolled in the study at 48, 72, and 96 weeks
- Quality of life in patients treated with inodiftagene vixteplasmid
- Assessment of safety

STUDY DESIGN:

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 US Food and Drug Administration (FDA) guidance. 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 transurethral resection (TUR), and then had all papillary disease completely resected and obvious CIS disease fulgurated when indicated. 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. 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%.

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

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 informed consent form
12. Patient must be able to comply with protocol requirements, including attendance at required clinic visits

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 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 have tested positive for human immunodeficiency virus (HIV). No HIV testing is required if patient is not known to have tested positive
9. Patient is female and is pregnant or breastfeeding
10. Patient has any medical, psychological, or social condition or situation that may, in the investigator's opinion, make it difficult for the patient to tolerate study medication or comply with study procedures and other requirements. This includes but is not limited to active infections, poorly controlled diabetes, uncontrolled cardiac arrhythmia, angina pectoris, or hypertension
11. Patient has a known presence or history of malignancy of other organ system within the 5 years before study start, with the exception of non-melanoma skin cancer (eg, basal cell carcinoma or squamous cell carcinoma of the skin); very low or low-risk prostate cancer (by National Comprehensive Cancer Network guidelines) defined as prostate-specific antigen <10 ng/dL, Gleason score ≤6, and clinical stage T1c; or patients who have been disease-free for at least 2 years following stage 1 or 2 cancer
12. Patient is on immunosuppressive therapy or has had a transplant within 12 months before study start, except for chronic use of corticosteroids (eg, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, or any other similarly chronic use of steroids)
13. Patient has any other significant disease that, in the opinion of the investigator, would prevent study entry

TEST PRODUCT(S), DOSE AND MODE OF ADMINISTRATION: BC-819 at 20 mg/50 mL, instilled intravesically into the bladder, with a retention time of at least 30 minutes (up to 2 hours)

DURATION OF STUDY: approximately 15 months of enrollment and 96 weeks of treatment

- Induction Phase (weekly treatments): 12 weeks; 10 weekly treatments followed by 2 weeks for initial assessment of primary endpoint of complete response in CIS patients

Maintenance Phase (treatment every 3 weeks): 84 additional weeks; assessment of EFS endpoint at 48 weeks (36 weeks after initiation of maintenance therapy); completion of therapy at 96 weeks

DISCONTINUATION FROM TREATMENT:

Reasons for permanent discontinuation include the following:

1. In patients with CIS at baseline, failure to clear CIS lesions by Week 12; however, patients who clear CIS lesions but have low-grade disease should continue treatment. Patients with CIS lesions that fail to clear may be followed by cystoscopy until they have a cystectomy or start an alternative treatment, but will be considered non-responders in the primary efficacy analysis
2. Recurrence or appearance of high-grade papillary lesions at the Week 12 cystoscopy or later or of CIS lesions after clearance. ***Only patients who meet the definition of recurrence should be discontinued. Patients with persistence or appearance of lower grade disease should not be discontinued***
3. Unacceptable toxicity, defined as a persistent Grade 3 adverse event (AE) or higher, as assessed by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, despite dosing delay and/or symptomatic treatment (according to the AE management guidelines in Section 9.5)
4. Withdrawal of consent

Any patient without tumor in the bladder but presence of tumor in the upper urinary tract will not be classified as a failure in the primary analyses and will continue study participation.

PRIMARY EFFICACY ENDPOINT:

The primary efficacy endpoint is, in patients with CIS at baseline, the:

- Proportion that achieves a complete response anytime on or after 12 weeks and within the first 48 weeks

Complete response in patients with CIS is defined as at least one of the following:

- Negative cystoscopy and negative (including atypical) urine cytology
- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology
- Negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative

The complete response in patients with CIS for this endpoint must be documented on or after the Week 12 response assessment and on or prior to the Week 48 assessment. Duration of complete response in CIS patients will be calculated from the documented onset of the complete response to the assessment where the patient no longer meets the definition of complete response. More generally, recurrence is defined as the reappearance or persistence of high-grade disease or new high-grade disease including CIS. Recurrence must be biopsy proven. Persistence, appearance, or presence of lower grade disease will not be considered recurrence.

SECONDARY EFFICACY ENDPOINTS:

The secondary endpoints include the following:

- The incidence of EFS at 48 weeks, where EFS is defined as high-grade recurrence-free survival (overall population and subgroup of patients with CIS)
- The incidence of EFS at 12, 24, 36, 72, and 96 weeks, where EFS is defined as high-grade recurrence-free survival (overall population and subgroup of patients with CIS)
- Time to recurrence; recurrence is defined as an EFS event
- The incidence of progression-free survival at 48, 72, and 96 weeks as well as time to progression estimated using Kaplan-Meir methods. Progression is defined as the development of T2 or

greater disease. Sensitivity analyses will also be performed and will include any of the following as progressions:

- An increase in stage from Ta or CIS to T1, or
- Development of T2 or greater, or
- Lymph node disease, or
- Distant metastasis

- Overall survival of patients enrolled in the study at 48, 72, and 96 weeks and survival time estimated using Kaplan-Meier methods
- Changes in quality of life over time, as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30; a general questionnaire for cancer) and the Non-Muscle Invasive Bladder Cancer Questionnaire (QLQ-NMIBC24; a specific questionnaire for NMIBC disease)

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

STATISTICAL ANALYSIS:

Analyses will generally be performed for the entire patient population, subgroups of patients with papillary lesions only, and patients with CIS (with or without papillary lesions). Determination of success for the treatment will be based on the full analysis set population of all treated patients. The primary endpoint will be analysed using a two-sided 95% binomial exact CI (Clopper-Pearson) for the rate of patients with baseline CIS who have a complete response.

Duration of response in CIS patients who have a complete response will be calculated using Kaplan-Meier methods starting from the documented onset of the complete response to the assessment where the patient no longer meets the definition of complete response..

In addition to time point analyses of rates of freedom from recurrence, Kaplan-Meier plots of recurrence-free survival will be calculated for all patients. Kaplan-Meier methods will also be used to estimate progression-free survival and overall survival rates at 48, 72, and 96 weeks.

The first 35 patients enrolled are to have CIS (with or without papillary disease). An interim futility analysis will be performed on these patients and if 9 or fewer of these patients have complete responses the study may be discontinued. Once the first 35 patients with CIS are enrolled and 10 or more complete responses are documented, enrollment may continue with the full study population (including patients with high-grade papillary disease without CIS who meet inclusion and exclusion criteria).

2. TABLE OF CONTENTS

3. TABLES

4. LIST OF ABBREVIATIONS

AE	adverse event
AUA	American Urological Association
BCG	bacillus Calmette-Guerin
CIS	carcinoma in situ
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DM	data manager
DS	drug substance
DTA	diphtheria toxin A
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EOS	end of study
FAS	full analysis set
FDA	US Food and Drug Administration
GCP	good clinical practice
HIV	human immunodeficiency virus
ICF	informed consent form
IEC	independent ethics committee
IMP	investigational medicinal product
IRB	institutional review board
ITT	intent to treat

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

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.

6. ETHICAL CONDUCT OF THE STUDY AND REGULATORY REQUIREMENTS

6.1 Institutional Review Board (IRB)

The study protocol and any amendments will be reviewed by an institutional review board (IRB). The IRB will review the informed consent form (ICF), any updates to the ICF, and any written materials provided to patients. A list of all IRBs and contact information will be included in the final clinical study report.

6.2 Ethical Conduct of the Study

This study will be conducted in accordance with the ethical principles that have their origins in the 2013 revision of the Declaration of Helsinki by the World Medical Association, in compliance with the approved protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

6.3 Patient Information and Consent

The investigator will obtain a written (signed and dated by the patient) ICF from every patient eligible to participate in this study. Obtaining an ICF involves providing the participant adequate information concerning the study, providing adequate opportunity for the participant to consider all options, responding to the participant's questions, ensuring that the participant has comprehended this information, obtaining the participant's voluntary agreement to participate, and continuing to provide information as the participant or situation requires. To be effective, the process should provide ample opportunity for the investigator and the eligible patient to exchange information and ask questions.

The investigator will also explain that eligible patients can decide to refuse to participate in this study or to withdraw from the study at any time and for any reason, without any consequences to his/her subsequent.

The patient will receive a copy of the patient information and the signed ICF.

The patient will be informed of any information that becomes available during the course of the study that may be relevant to his/her willingness to continue participation in the study.

Eligible patients participating in this study will be informed that a monitor or a health authority inspector, in accordance with applicable regulatory requirements, may review the portions of patient source records and source data related to the study. Data protection and confidentiality will be handled in compliance with local laws.

6.4 Protocol Revisions and/or Deviations

Changes to the protocol may be made only by the sponsor. Approval for amendments must be obtained before any such changes can be implemented, except for changes necessary to eliminate an immediate safety concern to study patients, or for changes that involve only logistical or administrative aspects of the study. No approval will be required for notifications.

Protocol modifications made to the IRB/independent ethics committee (IEC)–approved protocol or protocol amendment made for any reason by the investigator will constitute a protocol deviation, whether or not it is medically indicated.

6.5 Patient Insurance

The sponsor will maintain an insurance policy for the total duration of the study covering the patients and investigators with respect to the risks involved in conducting this study according to this protocol. The insurance policy will be filed in the investigator's file or can be made available to the investigator and to the IRB/IEC upon request.

6.6 Informing the Referring Physician

The investigator will inform the patient's primary care physician of his/her participation in the study by sending a letter to the physician.

7. INTRODUCTION

7.1 Bladder Cancer

Bladder cancer is a common illness, the ninth most common cancer worldwide and the fourth most common cancer in men in the United States. An estimated 79,030 new cases of bladder cancer are expected to occur in the United States in 2017. Bladder cancer incidence is about 4 times higher in men than in women and almost 2 times higher in Caucasian men than in African-American men (American Cancer Society 2016).

As most cases are detected early, the mortality rate for bladder cancer is only about 20% of its incidence, and its prevalence rate is high relative to its incidence rate. Death rates for urinary bladder cancer have been stable in men since 1987 and decreasing in women by 0.4% per year since 1986. An estimated 16,870 deaths from bladder cancer will occur in 2017.

Most bladder cancers are transitional cell carcinomas, and most are superficial (ie, do not penetrate the muscularis layer), hence the term non-muscle invasive bladder cancer (NMIBC). The estimated proportion of patients with bladder cancer that is non-muscle invasive in the US is 70% to 80% (Lamm 2002; Madeb et al. 2009; Shelley et al. 2010). Of these new NMIBC cases, approximately 70% are Ta (confined to bladder epithelium), 20% are T1 lesions (invasion of lamina propria), and 10% are Tis disease (carcinoma in situ [CIS] lesions). As much as 80% of patients with Ta disease can be expected to experience disease recurrence, and up to 45% of patients with T1 or CIS lesions will experience disease progression without treatment (van Rhijn et al. 2009).

7.1.1 Staging/Grading

Prognosis and treatment of bladder cancer depends on the tumor stage (depth of penetration into or through bladder wall combined with nodal and metastatic status) and other parameters, including prior recurrences, number and size of tumors identified, tumor grade, and presence or absence of CIS lesions (Sylvester et al. 2006). For definitions of staging and grading, see Table 9.1. NMIBC itself does not lead to mortality. However, if the tumor progresses and becomes invasive resulting in local progression or local or distant metastases, mortality increases considerably (Stein et al. 2001). In addition, treatment of invasive bladder cancer requires radical cystectomy and/or adjuvant chemotherapy with significant increase in morbidity.

The primary treatment approach to NMIBC is surgical therapy of resectable disease coupled with adjuvant therapy. Intravesical bacillus Calmette-Guerin (BCG) instillation has been the mainstay of treatment of intermediate- and high-risk NMIBC for several decades (Lamm 2002). It is used as an adjuvant after transurethral resection (TUR) of papillary carcinomas and for the treatment of CIS lesions. BCG has been shown to decrease progression as well as recurrence (Sylvester et al. 2002). Several chemotherapeutic agents, including mitomycin C, have also shown efficacy in certain groups of patients with NMIBC (Shelley et al. 2010). However, recurrence is the norm, with approximately 60% to 70% of patients experiencing recurrences after initial treatment and 25% progressing to invasive disease (Morgan et al. 2011). Hence, there is an established unmet medical need and new treatment agents are needed.

7.1.2 Bacillus Calmette-Guerin–Unresponsive Patients

While treatment with BCG has markedly reduced recurrence after TUR of papillary tumors and resolves CIS lesions in some patients, about 30% to 40% of patients eventually fail treatment with BCG (Zlotta et al. 2009). A subgroup of patients who fail BCG are considered "BCG-unresponsive." BCG-unresponsive patients with high-grade NMIBC must have been adequately treated with BCG. These patients include those who did not respond to BCG treatment and have persistent or recurrent CIS within 12 months after BCG was initiated, those with recurrent high-grade NMIBC within 6 months of their last intravesical treatment with BCG, or those with high-grade T1 disease at the first evaluation following induction (FDA 2018). Adequate treatment generally requires either at least 5 of 6 induction doses and at least 2 of 3 maintenance doses or at least 5 of 6 induction doses plus at least 2 of 6 doses of a second induction course. No intravesical or systemic agents are currently known to be effective for treatment of these patients so as to be considered standard treatment. Data from studies of gemcitabine in patients whose disease has failed BCG (Skinner et al. 2013; DiLorenzo et al. 2010) demonstrate a 2-year disease-free survival rate of approximately 20%, and data from studies of docetaxel (Laudano et al. 2010) are similar. Therefore, the currently recommended therapy for BCG-unresponsive NMIBC is cystectomy, either partial or radical (Yates et al. 2012). However, because of concomitant conditions, many patients are not candidates for major surgery such as cystectomy. These patients must currently rely on options with minimal effectiveness in this situation (eg, instillations of chemotherapeutic agents or repeat TURs [re-TURs]).

The US Food and Drug Administration (FDA) and the American Urological Association (AUA) convened a workshop to address the development of new therapies for patients with NMIBC (Jarow et al. 2014). The workshop participants addressed the BCG-unresponsive patient population. They agreed that there was no consensus standard-of-care approach for these patients apart from cystectomy and that no therapy could be agreed upon to serve as a control for randomized clinical studies in this setting. The participants recommended that single-arm Phase 2 studies could support regulatory approval for these patients. Moreover, for patients with CIS lesions, it was recommended that a study achieving at least a 30% recurrence-free survival at 18 to 24 months, with a sample size whose CI excluded a lower boundary of 20%, would be appropriate. This recommendation has provided, in essence, a road map to drug development and approval in this setting.

A more detailed FDA draft guidance document was published in November 2016 entitled *BCG-Unresponsive Non-Muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment: Guidance for Industry*, which re-states and extends the recommendations of the FDA/AUA workshop. The FDA recommends that early stage development of agents for NMIBC should involve demonstration of activity against extant disease, for example, in marker lesion studies. The guidance defines BCG-unresponsive patients as those with persistent high-grade NMIBC who have been adequately treated with BCG who did not respond to BCG treatment and have a new (if previously treated for a low-grade NMIBC) or persistent high-grade recurrence at or around 6 months after BCG was initiated, and those who despite an initial complete response to BCG, relapse with high-grade NMIBC within 6 months of their last intravesical treatment with BCG (Lerner et al. 2015). Furthermore, the guidance states that for patients with unresponsive NMIBC for whom no standard therapy apart from radical cystectomy

exists, a single-arm study design is appropriate, and the complete response rate and duration of complete response are relevant efficacy endpoints in patients with CIS.

The FDA guidance was finalized in February 2018 (FDA 2018). This guidance further emphasized the study of CIS patients in single-arm trials and provides more detailed definitions of BCG-unresponsive disease and adequate BCG therapy. The definition provided for the BCG-unresponsive population was clarified, with the Agency recommending that the definition of treatment failure apply to patients who had failed one induction and one maintenance course of BCG at a minimum. In addition, it specified that a single-arm trial in the BCG-unresponsive patient population should employ a primary endpoint of complete response in CIS patients. This guidance informs the design of this study of the investigational agent BC-819 for the BCG-unresponsive NMIBC population.

7.2 BC-819 Background

The biologically active ingredient of BC-819 (inodiftagene vixteplasmid) is a recombinant DNA plasmid (BC-819 drug substance [DS]) that directs the expression of a potent toxin specifically in malignant cells but not in normal tissue. It has been designed to exploit the established biology of the H19 gene, which is upregulated and expressed at high levels only in malignant cells, and to incorporate technology that enables the delivery of a sequence that encodes for a lethal bacterial toxin from diphtheria so that the toxin is specifically expressed and activated only in bladder cancer tissue. Uptake into malignant cells has been optimized by complexing the recombinant DNA plasmid with a transfection reagent (polyethylenimine [PEI]) to best facilitate entry of the recombinant molecule into cells. The resultant drug product (BC-819/PEI) is administered intravesically to enable maximal topical exposure with target bladder cancer cells.

H19 is a long non-coding RNA that has a restricted pattern of expression rendering it potentially useful for the targeted delivery of therapies to cancer (Matouk et al. 2013). H19 is an oncofetal RNA gene highly expressed in the placenta but not normally expressed in adult tissues (Matouk et al. 2005). However, its expression is upregulated in malignancy, and most human bladder cancers (Ohana et al. 1999; Luo et al. 2013) as well as in many other tumors. The abnormal upregulation of H19 expression in malignancy is at least partly consequent to alterations in transcription factor availability and activity, and the regulatory controlling sequences of the H19 promoter and enhancer that respond to these factors have been characterized (Kopf et al. 1998; Yoo-Warren et al. 1988; Ohana et al. 1999). Key transcription factors known to be deregulated in cancer and function as modulators of H19 promoter activity and H19 expression have been identified (including E2F, P53, HIF1, and Slug) (Berteaux et al, 2005; Dugimont et al, 1998; Wu et al. 2017, Matouk et al. 2014). Thus, these regulatory elements can be used to control cytotoxic gene expression in a manner that prevents transcription in normal tissues and drives expression at significant levels in malignant cells that express H19.

Diphtheria toxin is a potent cellular toxin and exhibits several characteristics that make it a favorable choice for anti-cancer transcriptional targeting. Its biology and mechanisms of action are well understood; it is a 58 kDa protein that catalyzes the transfer of an adenosine diphosphate-ribose group from nicotinamide adenine dinucleotide to the protein translation factor EF2, inhibiting all protein translation (Bell and Eisenberg 1996). Single copies of this toxin are lethal to a cell. Moreover, the inhibitory activity of the toxin is encompassed in the A chain (diphtheria toxin A [DTA] 21 kDa), while the B chain is necessary for cellular entry.

Thus, cellular introduction and expression of the gene encoding and expressing DTA is lethal to the target cell but not to surrounding cells.

BC-819 has been designed to exploit the specificity of H19 activation to express DTA in bladder cancer cells. BC-819 DS is a double-stranded DNA plasmid 4560 base pairs in length. It has been engineered using recombinant DNA technology so that 832 base pairs of H19 regulatory sequences (787 upstream and 45 downstream of the transcription start site) regulate the expression of DTA gene. These regulatory sequences have been shown to direct gene expression specifically in bladder cancer cells (Ohana et al. 2002; Ohana et al. 2004). The plasmid also contains the kanamycin-resistance gene that allows selection of plasmid-containing *Escherichia coli* bacterial cells so that the plasmid can be produced in large-scale bacterial cultures.

PEI is a cationic polymeric moiety that efficiently facilitates the entry of BC-819 into rapidly dividing cells and improves efficiency of transfection both in vitro and in vivo in a variety of cellular and animal models, including bladder cancer. It is complexed with the BC-819 DS in a fixed molar ratio during the manufacturing of the drug product. Experiments in vitro demonstrate that BC-819 complexed with PEI is efficiently taken into more than 85% of cells following a single transfection. In this protocol, the term BC-819 will hereafter be used to refer to the plasmid/PEI complex prepared for clinical administration.

When transfected into a tumor containing H19 expressing cells, BC-819 becomes transcriptionally active, producing RNA for DTA, which is then translated into the lethal diphtheria toxin. Following intravesical administration, cellular toxicity due to DTA expression is bladder cancer–specific. H19 is expressed in adults mostly in malignant tissue; thus, plasmid taken up in normal cells should remain unexpressed. In addition, due to the absence of the B chain subunit, if toxin is released from dying cells it is not taken up by other normal cells. Thus, BC-819 is a specifically targeted therapy for bladder cancer. Studies have demonstrated that BC-819 DNA is detectable after intravesical administration for more than 48 hours in urine and in bladder tumors in patients (Ohana et al. 2004) and that DTA transcription is detectable after intravesical administration in experimental rat bladder tumors (Ohana et al. 2004). In vitro studies have also confirmed that protein synthesis is inhibited in tumor cells transfected with BC-819 (Ohana et al. 2002; Ohana et al. 2004).

In animal models, BC-819 is active against bladder cancer. In an orthotopic rat tumor model (Ohana et al. 2004), it was shown that syngeneic bladder tumors (Nara Bladder Tumor No. 2 cells) growing in the bladder could be effectively treated with 2 intravesical administrations of BC-819. In vitro studies with this cell line confirmed that the mechanism of action is via the dose-dependent expression of DTA chain driven by the H19 regulatory sequencing. Additional studies employed a model of bladder carcinogenesis due to the ingestion of nitrosamine by rats. In this experimental model, rats reproducibly develop visible bladder tumors after approximately 20 weeks of nitrosamine dietary supplementation. Intravesical administration of BC-819 is effective in reducing mean tumor dimensions and weight and leads to complete eradication of tumors in some animals. These data formed the basis for the initial clinical development of BC-819 in patients with bladder cancer.

7.3 BC-819: Clinical Studies in Patients With Bladder Cancer

Two clinical studies (one Phase 1 study and one Phase 2 study) of the intravesical administration of BC-819 as a single agent have been completed to date in patients with NMIBC. Additionally,

a Phase 2 combination therapy study of the administration of BC-819 and BCG has also been completed.

7.3.1 Phase 1 Study

The initial Phase 1 study was a dose-escalation study that enrolled patients with recurrent low-grade NMIBC (Sidi et al. 2008). At entry in this study, patients underwent resection of all disease except 1 marker lesion 0.5 to 1.0 cm in size. Patients were then treated with intravesical BC-819 weekly for 3 weeks followed by a 1-week break and an additional 3 weekly treatments. Seven weeks later, patients who had not progressed were allowed to continue receiving maintenance therapy of BC-819 in 3 weekly instillations every 12 weeks. The response of the marker lesion was assessed at 12 weeks, and residual tumor was removed at that time. Resected tumors were assessed for H19 expression.

A total of 18 patients were treated with escalating doses by cohort of BC-819 at the 2-, 4-, 6-, and 12-mg dose (n=3 in each cohort) and at the 20-mg dose (n=6). Dose escalation was to continue until dose-limiting toxicity, defined as Grade 3 or worse (National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) adverse event (AE) at least possibly related to study medication, occurred during the first 3-week course of treatment or the immediate follow-up period before repeat dosing. The mean age of patients was 71 years (range: 49 to 82 years); 83% were male. Patients had a mean of 5 prior occurrences (range: 1 to 15 occurrences). Ten of 18 patients (56%) had ≥2 recurrences in the past 2 years. Seventeen patients (94%) had received prior BCG, and several patients had also received various chemotherapeutic agents.

No dose-limiting toxicities were observed or reported, and no deaths occurred during the study or during the follow-up period. Intravesical administration of BC-819 at doses from 2 mg to 20 mg plasmid weekly for 6 weeks was well tolerated. The most frequently reported AEs considered to be at least possibly related to investigational product for any dose cohort were mild to moderate in severity and were most commonly renal and urinary disorders. Mild bladder discomfort and dysuria were reported in 11.1% and 16.7% of patients, respectively. Moderate dysuria and micturition urgency were reported in 5.6 % and 16.7% of patients, respectively. Severe (Grade 3) micturition urgency was reported by 1 patient in the 6-mg dose cohort after the fourth intravesical treatment. In total, 44% of patients had a urinary tract infection during the study, of which 17% were considered related to other investigational procedures such as the video-cystoscopy, catheterization, or surgical resection. Mild (Grade 1) diarrhea, hypertension, and asthenia were reported in 11.1%, 16.7 %, and 11.1% of patients, respectively. Laboratory AEs considered possibly related to treatment included increased blood creatinine and leukopenia in 22.2% and 11.1% of patients, respectively. There was no dose-response relationship in overall AEs (related + nonrelated). One serious adverse event (SAE) considered possibly related to study treatment, urinary urgency requiring hospitalization, occurred in the study. This SAE occurred in a patient in the 6-mg weekly treatment group.

The primary efficacy assessment was overall response rate (complete and partial) as directly visualized by cystoscopy at Week 12; in 4 of 18 patients (22%), complete responses were observed. In an additional 4 of 18 patients (22%), partial responses were observed. Thus, total responses were observed in 8 of 18 patients (44%). Median time to recurrence among all 18 study patients and across all dosing levels was 5.7 months (95% CI was 4.1 to 11.6 months).

H19 expression was detected in all tumors at baseline. 12/18 (66.7%) of the patients were recurrence-free at 3 months, and 44.4% and 33.3% were recurrence-free at 12 months and 24 months respectively.

In summary, the maximum tolerated dose for weekly BC-819 administration was not identified, and 20 mg was identified as the dose for further study. Higher doses (>20 mg) could not be administered because of volume constraints. AEs were generally mild to moderate; most may have been related either to study drug or to the catheterization and treatment procedure. Anti-tumor activity was evident, and complete and partial responses against existing macroscopic tumors were observed. Although the sample size was small, there was no suggestion of a dose-response effect with regard to either efficacy or safety.

7.3.2 Phase 2 Monotherapy Study

Following the Phase 1 study, a Phase 2 study of BC-819 was completed in patients with superficial bladder cancer of intermediate risk. The primary endpoint in this study was to determine tumor recurrence in resected patients; a secondary endpoint was response rate of marker lesions. Patients with histologically confirmed superficial bladder cancer with recurrent stage Ta (any grade) or T1 (low-grade) NMIBC were eligible to enter the study. Patients with CIS lesions were excluded. All tumor specimens resected at baseline were H19 positive. Patients must have failed at least 1 prior conventional therapy including either BCG or chemotherapy and, as in the Phase 1 study, have 1 tumor ≤1.0 cm in diameter to serve as a "marker" tumor after removal of all other tumors. Treatment in this study was composed of an initial induction phase of 6 weekly 20-mg instillations followed by safety and efficacy assessment at Week 9. Subsequently, in the absence of recurrence or toxicity requiring discontinuation of therapy, these patients continued to receive maintenance therapy of 3 weekly courses every 12 weeks.

A total of 47 patients were treated in this study; 38 patients (81%) received prior BCG, and more than half of the patients received other therapies as well (45% of patients received 2 or more prior treatments). Eight patients were not evaluable due to protocol violations and early withdrawal.

At the time of primary assessment at Week 9 after the start of treatment, 13 patients (28% of the intent-to-treat [ITT] population and 33% of the per-protocol population) had complete disappearance of the marker lesion, and no new lesions were reported. Twenty-six patients (55%) in the ITT population and 64% of patients in the per-protocol population had no new lesions at 3 months (the primary endpoint). Median time to recurrence for both the ITT and per-protocol populations was 11.3 months; 46% and 36% of patients were free of recurrence at 12 and 18 months, respectively, and 33% remained recurrence-free at 24 months follow-up. Treatment was very well tolerated. No patients discontinued because of treatment-related adverse events (TEAEs).

The most commonly reported AEs were renal and urinary disorders, experienced by 30% of patients entered. These included urinary frequency (15%), dysuria (11%), micturition urgency (6%), and urinary retention (6%). Urinary tract infections, classified under infections and infestations, were reported by 11% of patients. Other AEs experienced by 3 or more patients included increased blood potassium (11%) and asthenia, chills, pyrexia, and nausea (6%, each). No patients had an elevation of either creatinine or blood urea nitrogen levels.

Seven SAEs in 5 patients were reported: 1 patient developed urinary retention and a urinary tract infection and subsequently underwent TUR of the prostate; 1 patient developed a myocardial infarction; 1 patient developed hematuria; 1 patient developed pneumonia; and 1 patient had an exacerbation of pre-existing chronic obstructive pulmonary disease. Only the event of hematuria was considered by the treating investigator to be possibly related to study treatment, though also probably related to study procedure. SAEs in the other 4 patients were considered unrelated to study medication or procedure; 2 patients were screen failures who never received any study drug.

7.4 Phase 2 Combination Study

Additionally, a Phase 2 study was completed in 38 patients eligible for BCG treatment. Three different combination schedules were evaluated with a primary objective of evaluating the safety of the combination. All 3 schedules were well tolerated, with 3 SAEs reported, none of which was considered related to BC-819.

Tumor recurrence rate and progressive disease rate were not statistically significantly different among the 3 regimens. The overall recurrence-free survival rate was 54%, and the progression-free survival (PFS) rate was 75%. At 18 months of follow-up, the median time to recurrence and its confidence limits could not be calculated according to Kaplan-Meier survival analysis because a large percentage of patients had no recurrence. Because of the small number of patients, the optimal schedule could not be determined.

The safety and tolerability of combined therapy with BC-819/PEI and BCG were determined by reported AEs, physical examinations, vital signs, and laboratory tests. Patients who received any study medication (even a partial dose) were considered evaluable for safety.

Administration of BC-819/PEI+BCG was well tolerated. Overall, 65.8% (25/38) of patients experienced AEs during the study. The incidence of AEs was similar among the treatment groups and most AEs were mild. The most common AEs were renal and urinary disorders. The incidence of BC-819/PEI-related AEs was lower than that of BCG-related AEs (10.5% vs 26.3%). Only 1 patient had a procedure-related AE (pain in extremity). No patients withdrew because of AEs.

Three SAEs occurred during the study. None of them were related to BC-819/PEI or to BCG or to the procedure. Two of the SAEs, mild palpitations and moderate urinary tract disorder, resolved without sequelae. One patient had severe pulmonary edema that resulted in death.

7.5 Rationale for Study

The population for this study is patients with high-risk NMIBC whose disease is unresponsive to BCG. This is a patient population for which treatment options are limited and outcomes are usually poor. As reviewed above, patients whose disease is unresponsive to BCG have poor options for medical therapy, with outcomes suggesting 2-year disease-free survival ranging from 2% to 20%. Standard of care is therefore radical cystectomy. As summarized above, the AUA and FDA jointly convened a workshop to address the development of new therapies in NMIBC, specifically addressing patients who have repeatedly failed BCG therapy (Jarow et al. 2014). In November 2016, the FDA issued a second, more detailed guidance document for drug development in this specific population, which was finalized in February 2018. These guidance

documents state that for such patients, no standard of care could be identified that would serve as a control population for a randomized clinical study. Therefore, in this setting, a single-arm Phase 2 clinical study with complete response rate as the primary endpoint can provide primary evidence of effectiveness to support a marketing application. This Phase 2, single-arm, open-label study of BC-819 in patients who have high-risk NMIBC that is unresponsive to BCG has been designed with these guidelines in mind.

The Phase 1/2 and Phase 2 studies described above provide preliminary clinical evidence in support of this study. While the Phase 2 study patients did not fit the definition of BCG-unresponsive used in the proposed study, these patients were still quite heavily pretreated, with more than half of the patients receiving not only BCG but, in most cases, cytotoxic drugs as well; 45% had received 2 or more prior therapies. Furthermore, 67% had experienced 2 or more prior recurrences in the 2 years before study start. By ITT analysis of all patients entered in the Phase 2 study, median time to recurrence was 11.3 months (95% CI of 5.3 to 7.2 months). Forty-six percent (46%) of the ITT population was free of recurrence at 12 months.

The primary endpoint of this study will be to determine in patients with baseline CIS, the proportion of patients that experiences a complete response (CR). In this study, in accordance with the FDA guidance, complete response is defined as negative urine cytology and no lesions visible on cystoscopy, negative urine cytology with biopsy proven benign or low-grade NMIBC, or negative cystoscopy with malignant urine cytology, if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative. Additionally, the duration of the response will be determined. Recurrence is defined as the reappearance or persistence of high-grade disease. Recurrence must be biopsy proven. Persistence, appearance, or presence of lower grade disease will not be considered recurrence. 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 failures, as will patients with CIS at baseline whose CIS lesions have not resolved by the 12-week cystoscopy or who have CIS or high-grade papillary disease at later timepoints.

High-risk recurrences are the most important predictors of risk of tumor progression. Patients who recur with only low-grade recurrence will not be considered treatment failures and may continue study participation after standard-of-care resection of the new lesion(s), if any. Sylvester et al. (2006) developed a model for predicting recurrence and progression in NMIBC. In this model, which included tumor grade, low-grade tumors, there was a low potential for progression. Fernandez-Gomez et al. (2009) used a similar approach and considered a population in which all patients had been treated with BCG. These analyses demonstrated that high-grade tumor was a moderate risk factor for recurrence but a very strong risk factor for progression. Conversely, presence of low-grade tumor had little effect on progression. Therefore, the primary target population for this study focuses on patients with elevated risk for progression and comprises patients with high-risk/grade NMIBC that is BCG-unresponsive.

8. STUDY OBJECTIVES

8.1 Primary Objectives

The primary objective is to determine, for the patients with baseline CIS:

- The proportion that achieves a complete response (CR) after treatment with inodiftagene vixteplasmid

8.2 Secondary Objectives

The secondary objectives are to determine the:

- Proportion of patients with absence of high-grade recurrent or persistent disease at 48 weeks (overall population and subgroup of patients with CIS)
- Proportion of patients with absence of high-grade recurrent or persistent disease at 12, 24, 36, 72, and 96 weeks (overall population and subgroup of patients with CIS)
- Time to recurrence (Kaplan-Meier plot)
- Proportion of patients who are progression-free at 48, 72, and 96 weeks
- Overall survival of patients enrolled in the study at 48, 72, and 96 weeks
- Quality of life in patients treated with inodiftagene vixteplasmid
- Assessment of safety

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

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

9. Patient is female and is pregnant or breastfeeding
10. Patient has any medical, psychological, or social condition or situation that may, in the investigator's opinion, make it difficult for the patient to tolerate study medication or comply with study procedures and other requirements. This includes but is not limited to active infections, poorly controlled diabetes, uncontrolled cardiac arrhythmia, angina pectoris, or hypertension
11. Patient has a known presence or history of malignancy of other organ system within the 5 years before study start, with the exception of non-melanoma skin cancer (eg, basal cell carcinoma or squamous cell carcinoma of the skin); very low or low-risk prostate cancer (by National Comprehensive Cancer Network guidelines) defined as prostate-specific antigen <10 ng/dL, Gleason score ≤6, and clinical stage T1c; or patients who have been disease-free for at least 2 years following stage 1 or 2 cancer
12. Patient is on immunosuppressive therapy or has had a transplant within 12 months before study start, except for chronic use of corticosteroids (eg, rheumatoid arthritis, asthma, chronic obstructive pulmonary disease, or any other similarly chronic use of steroids)
13. Patient has any other significant disease that, in the opinion of the investigator, would prevent study entry

9.4 Study Treatment Plan

9.4.1 Enrollment Period

At study entry, patients with BCG-unresponsive disease can have completely resected papillary disease, resected papillary disease with CIS, or CIS alone. It is required that the first 35 patients treated have CIS (with or without papillary disease).

To fully define the extent of disease at study entry, eligible patients must have had a recent TUR (within 6 weeks/42 days) prior to start of treatment. No more than 42 days may elapse between complete resection of papillary disease and start of therapy. Patients with T1 disease should undergo resection at the base of the lesion to ensure the absence of muscle-invasive disease. Patients for whom the last TUR was performed by a study investigator (or an on-site designee) ≤42 days before the first study treatment are not required to have a re-TUR. It is recommended that patients who had a TUR performed elsewhere and/or patients with high-grade disease at baseline (high-grade Ta, high-grade T1, or Tis) have a re-TUR performed ≤42 days before the first study treatment to exclude any visibly growing stage Ta or T1 papillary tumors (in which case, re-TUR is indicated), remaining CIS lesions, and/or exclude T2 (muscle-invasive) disease. Any visible CIS lesions should be fulgurated at that time as needed.

Patients should be staged before enrollment. Staging should include the use of bladder mapping and random biopsies in patients with CIS or high-grade papillary disease (Gudjonsson et al. 2012). In this study, tumor staging will be conducted in accordance with the AUA-adopted TNM staging classification (Sobin et al. 2009), and grading will follow the World Health Organization (WHO) grading classification (2004 revision, Miyamoto et al. 2010) with tumors categorized as papillary urothelial neoplasm of low malignant potential, low-grade, or high-grade. TNM classifications are shown in Table 9.1.

Urine cytology results should also be obtained and evaluated prior to enrollment.

Table 9.1. TNM Staging Classifications

T - Primary Tumor	N – Lymph Nodes	M - Distant Metastasis
Ta: Noninvasive papillary carcinoma	Nx: Regional lymph nodes cannot be assessed	M0: No distant metastasis
Tis: Carcinoma in situ	N0: No regional lymph node metastases	M1: Distant metastasis
T1: Tumor invades sub-epithelial connective tissue	N1: Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
T2: Tumor invades muscularis • T2a: Superficial muscle (inner half) • T2b: Deep muscle (outer half)	N2: Metastasis in multiple lymph nodes in the true pelvis	
T3: Tumor invades peri-vesical tissue (beyond muscularis) • T3a: Microscopically • T3b: Macroscopically (extravesical mass)	N3: Metastasis in a common iliac lymph node	
T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall • T4a: Prostate, uterus, vagina • T4b: Pelvic wall, abdominal wall		

Source: Sobin et al. 2009.

Administration of BC-819 During Treatment Sessions

During treatment sessions, patients are encouraged to minimize fluid intake for 6 hours before instillation of the study medication and for 2 hours thereafter or until voiding, whichever comes first.

At each treatment session, a thin, sterile tube (called a Foley catheter) will be inserted into the bladder to drain urine and serve as a port of entry for the planned bladder instillations. Size 12-Fr (1 "French" or "Fr" = 0.33 mm = .013") catheters are normally suggested, but use of other sizes is acceptable per the investigator's discretion. Should the patient have an enlarged prostate (eg, benign prostatic hyperplasia) or any other condition that may obstruct the urethra, a Coudé-tipped catheter (called a Tiemann catheter) angled upward at the tip may be used to assist in negotiating the upward bend in the male urethra in order to completely drain the bladder. Size 10-Fr catheters are normally suggested for this scenario, but use of other sizes is acceptable. A 20-mg dose of BC-819 in a total volume of 50 mL will then be instilled into the bladder over approximately 4 minutes. After infusion, a further saline/sterile water flush may be needed to ensure that the BC-819 sitting in the catheter tubing is also flushed into the bladder space ensuring that full dose is delivered. The drug should be retained in the bladder for as long as possible (for a maximum of 2 hours but not less than 30 minutes) to allow for good topical contact between the drug and the inner bladder epithelium, which results in improved penetration (also referred to as plasmid transfection) of the drug into the cells through 1 or more bladder inner wall layers. The time that the instillation is completed and the time of postdose voiding should be recorded in the source documents.

9.4.2 Induction Phase

Study treatment will start within 7 days of enrollment and ≤42 days from the last TUR or biopsy. Initial therapy begins with a 10-week induction phase. Patients will receive an intravesical installation of BC-819 20 mg/50 mL once per week for 10 weeks during this phase.

9.4.3 Maintenance Treatment

Upon completion of the induction phase, patients will transition to a maintenance therapy schedule of BC-819 (ie, once every 3 weeks). The first maintenance treatment and visit will occur 12 weeks after enrollment (Visit 11). Treatments will continue every 3 weeks for 84 additional weeks until the end of the study (end of study [EOS] Visit 39) at 96 weeks.

Patients who have recurred with high-grade papillary carcinoma or with metastatic disease will be considered treatment failures and will be withdrawn from the study. All suspected recurrences (by direct visualization) must be documented by biopsy results.

Patients who are free of high-grade tumors or who are tumor-free (ie, patients benefiting from treatment) will be allowed to continue to receive maintenance therapy every 3 weeks per the schedule of treatment during the maintenance phase (Table 12.2 and Table 12.3) as long as response status is maintained and they are not considered a treatment failure.

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 of the study.

All enrolled patients will complete the following quality of life questionnaires at the visits indicated in the study schedule (Table 12.1 and Table 12.2):

- The European Organization for Research and Treatment of Cancer quality of life Questionnaire (EORTC QLQ-C30; a general questionnaire for cancer)
- Quality of Life Questionnaire–Non-Muscle-Invasive Bladder Cancer Questionnaire (QLQ-NMIBC24; a specific questionnaire for NMIBC disease)

The end of the study will be the 96-week visit (Visit 39) for all patients.

Maintenance Treatment and Repeat Direct Visualization Schedule

Patients benefiting from treatment with no documented progression or high-grade recurrence will continue to receive maintenance therapy every 3 weeks starting from Visit 11 (Week 12) onward.

During the first-year maintenance treatment, patients will continue treatment with BC-819 every 3 weeks as listed below:

- Visit 11 or 12 weeks (3 months)
- Visit 12 or 15 weeks
- Visit 13 or 18 weeks
- Visit 14 or 21 weeks
- Visit 15 or 24 weeks (6 months)
- Visit 16 or 27 weeks
- Visit 17 or 30 weeks
- Visit 18 or 33 weeks
- Visit 19 or 36 weeks
- Visit 20 or 39 weeks
- Visit 21 or 42 weeks
- Visit 22 or 45 weeks
- Visit 23 or 48 weeks (12 months)

As mentioned above, urine cytology, cystoscopy, and re-TUR (as needed for cause) will be performed every 12 weeks (within 2 weeks prior to the maintenance treatment) during the first year of the study (in alignment with the AUA standard of care) and are required before the maintenance treatment at the following visits:

- Visit 11 or 12 weeks (3 months)
- Visit 15 or 24 weeks (6 months)
- Visit 19 or 36 weeks
- Visit 23 or 48 weeks (12 months)

The 12-week visit (Visit 11) will include the initial evaluation of the primary endpoint of complete response rate in CIS patients.

During the second year of maintenance treatment, patients will continue treatment with BC-819 every 3 weeks as listed below:

- Visit 24 or 51 weeks
- Visit 25 or 54 weeks
- Visit 26 or 57 weeks
- Visit 27 or 60 weeks
- Visit 28 or 63 weeks
- Visit 29 or 66 weeks
- Visit 30 or 69 weeks
- Visit 31 or 72 weeks (18 months)
- Visit 32 or 75 weeks
- Visit 33 or 78 weeks
- Visit 34 or 81 weeks
- Visit 35 or 84 weeks
- Visit 36 or 87 weeks
- Visit 37 or 90 weeks
- Visit 38 or 93 weeks
- Visit 39 or 96 weeks (24 months) – end of study assessments with no treatment

Mandatory second year cystoscopy should be performed within 2 weeks prior to the following visits and is required before the maintenance treatment:

- Visit 27 or 60 weeks
- Visit 31 or 72 weeks (18 months)
- Visit 35 or 84 weeks
- Visit 39 or 96 weeks (24 months)

9.5 Dosing Delays

All toxicity in this study will be graded in accordance with CTCAE guidelines (version 5.0).

- No dose reduction of BC-819 is planned
- No dose adjustments are allowed
- A delay of up to 2 weeks from the scheduled treatment (≤2 weeks) is allowed at the investigator's discretion
- Administration of any missed doses should be discussed with and approved by the sponsor medical monitor or delegate
- Skipped doses or termination of treatment will be based on the observed toxicities (as specified below)

Grade 3 to 4 BC-819 related or unrelated AEs should be managed as follows:

- First occurrence of Grade 3 or 4 toxicity—withhold treatment until toxicity has improved to Grade ≤1
- Second occurrence:

  - Of Grade 3 toxicity—withhold treatment until toxicity has improved to Grade ≤1
  - Of Grade 4 toxicity—permanently discontinue treatment
- Third occurrence of Grade 3 toxicity—permanently discontinue treatment

Types of AEs that would warrant withholding treatment include but are not necessarily limited to persistent irritative symptoms lasting >48 hours, fever >100°F (37.8°C), sepsis, and hematuria. Patients should be reassessed at 1-week intervals until the applicable AE has resolved, up to a maximum delay of 5 weeks.

During the induction phase, the investigator may skip only 1 scheduled induction treatment because of a toxicity-related delay without disqualifying the patient from the study and warranting study withdrawal. All enrolled patients must receive a minimum of 5 of the planned 6 induction phase BC-819 instillations. Patients requiring more than 1 scheduled induction treatment to be skipped will require sponsor medical monitor or delegate approval to continue study participation. During the maintenance phase of the study, investigators may withhold treatment because of Grade 3 or 4 toxicity for 1 visit only.

9.6 Discontinuation of Therapy

Reasons for permanent discontinuation include the following:

1. In patients with CIS at baseline, failure to clear CIS lesions by Week 12; however, patients who clear CIS lesions but have low-grade disease should continue to be treated. Patients with CIS lesions that fail to clear may be followed by cystoscopy until they have a cystectomy or start an alternative treatment, but will be considered non-responders in the primary efficacy analysis
2. Recurrence of high-grade papillary lesions at the Week 12 cystoscopy or later or of CIS lesions after clearance. ***Only patients who meet the definition of recurrence should be discontinued. Patients with persistence or appearance of lower grade disease should not be discontinued***
3. Unacceptable toxicity, defined as a persistent Grade 3 AE or higher despite dosing delay (according to the AE management guidelines in Section 9.5)
4. Withdrawal of consent

Any patient without tumor in the bladder but presence of tumor in the upper urinary tract will not be classified as a failure in primary analyses and will continue study participation.

The reason for early discontinuation must be documented in the electronic case report form (eCRF). After discontinuation of study treatment for any reason, patients should be followed up for 30 days to assess safety.

10. STUDY PRODUCT

10.1 Study Medication Supply

BC-819 will be supplied by the study sponsor.

Study product is manufactured in accordance with current good manufacturing practices; the recombinant plasmid of BC-819 is manufactured by Boehringer-Ingelheim RCV, Vienna, Austria, and the transfection agent (PEI) by ChemCon GmbH, Freiburg, Germany.

10.2 Description of Study Product

BC-819 vials contain a 5- mL dose of BC-819 at a concentration of 0.4 mg plasmid/mL in 5% trehalose solution.

10.3 Packaging and Labeling

BC-819 is supplied as a single ready-to-use vial containing 50 mL BC-819 active plasmid and transfection agent complex at a concentration of 0.4 mg plasmid/mL in 5% trehalose solution. The product will be labelled according to local and national regulatory requirements.

10.4 Conditions for Storage and Use

BC-819 must be stored in a temperature-controlled and monitored environment at 2ºC to 8ºC.

10.5 Method of Assigning Patients to Treatment Groups

This is a single-arm study. All patients will receive BC-819 according to the schedules shown in Section 12 (Table 12.1, Table 12.2, and Table 12.3).

10.6 A Dispensing, Compliance and Accountability

All study medications will be administered in the clinic under the supervision of the investigator or his/her delegate. Accordingly, compliance and accountability will be assessed from records of administration maintained by the investigational study team at each site.

The investigator is responsible for maintaining accountability for the receipt, dispensing, and return of all study medication. Maintenance of all required investigational medicinal product (IMP) records can be delegated by the investigator to a suitably qualified member of the investigational study team at each site.

10.7 Concomitant Therapy

Patients may not receive other therapy for bladder cancer, either intravesical or systemic, except for anticholinergic treatment and/or chronic use of corticosteroids.

Patients may receive therapy for AEs per investigator judgment.

All concomitant medications, whether for TEAEs or other reasons, and the indications for their use must be recorded in the patient's eCRF.

11. EFFICACY AND SAFETY ASSESSMENTS

11.1 Primary Efficacy Variable

The primary efficacy endpoint is, in patients with CIS at baseline, the:

- Proportion that achieves a CR at any time on or after week 12 and within the first 48 weeks

Complete response is defined as at least one of the following:

- Negative cystoscopy and negative (including atypical) urine cytology
- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology
- Negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative

The complete response in patients with CIS for this endpoint must be documented on or after the Week 12 response assessment and on or prior to the Week 48 assessment. Duration of complete response in patients with CIS will be calculated from the documented onset of the complete response to the assessment where the patient no longer meets the definition of complete response. More generally, recurrence is defined as the reappearance or persistence of high-grade disease, or new high-grade disease. Recurrence must be biopsy proven. Persistence, appearance, or presence of lower grade disease will not be considered recurrence.

11.2 Secondary Efficacy Variables

The secondary endpoints include the following:

- The incidence of EFS at 48 weeks, where EFS is defined as high-grade recurrence-free survival (overall population and subgroup of patients with CIS)
- The incidence of EFS at 12, 24, 36, 72, and 96 weeks, where EFS is defined as high-grade recurrence-free survival (overall population and subgroup of patients with CIS)
- Time to recurrence; recurrence is defined as an EFS event
- The incidence of PFS at 48, 72, and 96 weeks as well as time to progression estimated using Kaplan-Meir methods. Progression is defined as the development of T2 or greater disease. Sensitivity analyses will also be performed and will include any of the following as progressions:
    - An increase in stage from Ta or CIS to T1, or
    - Development of T2 or greater, or
    - Lymph node disease, or
    - Distant metastasis
- Overall survival of patients enrolled in the study at 48, 72, and 96 weeks and survival time estimated using Kaplan-Meier methods

- 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

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:

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

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

12. STUDY PROCEDURES AND FLOWCHARTS

The administration of BC-819 is separated into 2 phases, the induction phase and the maintenance phase.

During the induction phase, eligible patients will receive BC-819 once per week for 10 consecutive weeks. The flow chart for the induction phase is Table 12.1.

During the maintenance phase, patients will transition to once every 3 weeks administration of BC-819 and will be evaluated every 12 weeks by cystoscopy for staging of response in order to determine continued participation. The urine cytology and cystoscopy must be completed within 14 days prior to the next administration of BC-819 and fully evaluated before initiating the treatment. The flow charts for the maintenance phase are Table 12.2 and Table 12.3.

In each of the the study flow charts, a study week is defined as 7 days. A description of each procedure is in Section 12.1. End of study procedures are required within 4 weeks of leaving the study.

Table 12.1 Induction Phase

Visit	Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10
Day	**≤42 days before V1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**
Baseline only procedures	X										
Interim physical examination including ECOG performance status	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Complete blood count and biochemical profile	X										
Urine sample for urinalysis (routine and microscopic)	X										
Urine sample for culture and sensitivity	X										
Urine sample for cytology	X										
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Biopsy	X										
Cystoscopy	X										
TUR/re-TUR	X										
QOL assessment		X									
Administration of BC-819		X	X	X	X	X	X	X	X	X	X

Detailed descriptions of procedures and timing are in Section 12.1.
Abbreviations: BC-819 = recombinant DNA plasmid complexed with polyethylenimine; ECOG = Eastern Cooperative Oncology Group; QOL = quality of life; re-TUR = repeat transurethral resection; TUR = transurethral resection; V = visit.

Table 12.2 Maintenance Treatment Through Visit 23 (Week 48)

Visit	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**
Week	**12 Day 84**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**
Interim physical examination including ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete blood count and biochemical profile	X				X								X
Urine sample for urinalysis (routine and microscopic)	X				X								X
Urine sample for culture and sensitivity	X				X								X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X

Maintenance Treatment Through Visit 23 (Week 48)

Visit	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**
Week	**12 Day 84**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**
Mandatory response assessment for patients with CIS	X				X[a]				X[a]				X[a]
Urine sample for cytology (must be completed within 14 days prior to BC-819 administration)	X				X				X				X
Cystoscopy (must be completed within 14 days prior to BC-819 administration)	X				X				X				X
TUR/re-TUR/biopsy as clinically indicated	X				X				X				X
QOL assessment				X								X	
Administration of BC-819	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Mandatory in patients who have not previously achieved a CR in their baseline CIS.

Detailed descriptions of procedures and timing are in Section 12.1.

Abbreviations: BC-819 = recombinant DNA plasmid complexed with polyethylenimine; CIS = carcinoma in situ; ECOG = Eastern Cooperative Oncology Group; QOL = quality of life; re-TUR = repeat transurethral resection; TUR = transurethral resection; V = visit.

Table 12.3 Maintenance Treatment Through Visit 39 (Week 96)

Visit	V24	V25	V26	V27	V28	V29	V30	V31	V32	V33	V34	V35	V36	V37	V38	V39/EOS
Week	**51**	**54**	**57**	**60**	**63**	**66**	**69**	**72**	**75**	**78**	**81**	**84**	**87**	**90**	**93**	**96**
Interim physical examination including ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete blood count and biochemical profile								X								X
Urine sample for urinalysis (routine and microscopic)								X								X
Urine sample for culture and sensitivity								X								X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for cytology (must be completed within 14 days prior to BC-819 administration)				X				X				X				X
Cystoscopy (must be completed within 14 days prior to BC-819 administration)				X				X				X				X
TUR/re-TUR/biopsy as clinically indicated				X				X				X				X
Administration of BC-819	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Detailed descriptions of procedures and timing are in Section 12.1.

Abbreviations: BC-819 = recombinant DNA plasmid complexed with polyethylenimine; ECOG = Eastern Cooperative Oncology Group; EOS = end of study; re-TUR = repeat transurethral resection; TUR = transurethral resection; V = visit.

12.1 Description of Study Procedures

The following procedures will be performed at the times noted in Table 12.1, Table 12.2, and Table 12.3.

Baseline tests for evaluating eligibility will include the following:

Informed consent: All patients must sign the ICF. Consent by a guardian is not acceptable unless the patient is unable to sign because of a physical problem with a hand or arm. In that case, the patient must give verbal consent, which must be witnessed by an observer not directly involved in the study. Patients who are not mentally competent to consent on their own are not permitted to participate in the study. The consent process must be properly documented in the source data.

Medical History and Physical Examination: Full medical history, including details of bladder cancer diagnosis, treatment and course, and physical examination during screening; directed physical examination of pertinent systems and interim history at other visits. Patients will be weighed at screening, at the start of maintenance therapy visit, and at EOS; weight is to be recorded in kilograms. Height will be collected only at baseline physical examination.

Electrocardiogram: a 12-lead electrocardiogram (ECG) will be performed at baseline for patients with a history or symptoms of cardiac or respiratory abnormality 12-lead if not performed within 1 month of study entry. Results from an ECG performed before study entry must be available for review by the investigator or his/her designee; a report alone is not adequate.

Chest X-Ray: Posterior-anterior and lateral chest x-ray, will be performed at baseline if not performed within 6 months before study entry. Results from a chest x-ray performed before study entry must be available for review by the investigator or his/her designee; a report alone is not adequate.

Urine Pregnancy Test: For women of childbearing potential only. Women who are at least 3 months past surgical sterilization and those with no menstruation for at least 12 months prior to entering the study are no longer considered to be of childbearing potential.

Interim Physical Examination: Examination of pertinent systems (ie, abdomen, back, and systems about which patient notes symptoms currently or at previous visit). Weight is to be recorded in kilograms at the start of maintenance therapy visit and at EOS.

In conjunction with the physical examination, ECOG performance status will be collected at screening and at each study visit.

Table 12.4 Eastern Cooperative Oncology Group Performance Status: Scored 0 (Normal Function) through 5 (Dead)

ECOG PERFORMANCE STATUS[a]	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

[a] Oken et al. 1982.

Vital Signs: Pulse, respiratory rate, systolic and diastolic blood pressure, and temperature (in °C) will be recorded at all visits. At treatment visits, vital signs should be recorded within 30 minutes prior to starting treatment.

Complete Blood Count/Biochemical Profile: Complete blood count includes hemoglobin, total red cell count, total white blood cell (WBC) count, absolute values for individual WBC types, and platelet count.

Biochemical profile will include, at a minimum, albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, (total) bilirubin, blood urea nitrogen, calcium, chloride, creatinine, glucose, potassium, sodium, and total protein.

Urinalysis: At visit indicated, urinalysis will include the following:

Routine: blood, leukocytes, glucose, ketones, nitrites, pH, protein, and specific gravity

Microscopic: WBC, red blood cells, bacteria, epithelial cells, crystals (with type identified), and mucus

Urine for Culture and Sensitivity: A urine sample will be collected for culture and sensitivity analysis at each visit indicated.

Urine cytology: The urine sample for cytology testing should be collected and analysed within 14 days prior to scheduled treatment administration.

Adverse Events: Patients will be questioned regarding the occurrence or resolution of AEs. Details regarding collection and assessment of AEs are given in Section 11.3.2 of this protocol.

Prior and concomitant medications: At baseline, a complete history of all treatment for bladder cancer, as well as all medications (both prescription and over the counter) should be recorded, including medication prescribed and over the counter and taken within 30 days before the screening visit, which will be recorded in the eCRF. During the study, all medications, both prescription and over the counter, are to be recorded in the eCRF. Indications for each medication should be collected, including whether the medication was taken prophylactically or therapeutically. Complete dosing information (dosage and actual number of doses taken each day) for all medications taken during the study are to be recorded.

Biopsy: Biopsy is required at baseline. Otherwise, biopsy is only needed if either cystoscopy or cytology result is positive. At baseline, site-directed mapping biopsies of normal appearing mucosa and any suspicious flat or papillary lesions must be performed. A sample of the resected tumors should be made available for local pathology review and study documentation.

Cystoscopy: Cystoscopy will be performed at the predetermined visits as indicated in the study schedules (Table 12.1, Table 12.2, and Table 12.3) with a consistent imaging technique when possible. Enhanced imaging (eg, blue-light or narrow band) is preferred when available. Cystoscopy should be performed within 14 days prior to scheduled treatment administration.

All interior surfaces of the bladder will be examined systematically, and observations will be recorded. Any suspicious lesions viewed during cystoscopy should be clearly indicated on a bladder diagram attached to the source document and numbered. Any biopsy specimens taken during cystoscopy should be immediately fixed in formalin, identified by patient's name, identification code, specimen number, and date (in accordance with the number assigned on the bladder diagram) and submitted for histopathology processing and evaluation at the local hospital pathology laboratory.

A complete description of visual findings must be documented in the eCRF. Should recurrent papillary tumors (of any stage or grade) or new CIS lesions be visualized in cystoscopy, a re-TUR procedure is indicated to resect all visible papillary tumors and fulgurate all CIS lesions that did not clear when indicated. All resected specimens are to be examined for exclusion of T2 or muscle invasive disease.

Transurethral Resection: Transurethral resection or repeat of previous TUR should be done as indicated in the study schedules by direct visualization.

Quality of Life Questionnaires Quality of life will be assessed via the EORTC QLQ-C30 (a general questionnaire for cancer) and the QLQ-NMIBC24 (a specific questionnaire for NMIBC disease) for all patients according to the study procedures flow charts (Table 12.1, Table 12.2, and Table 12.3). The results will be recorded in the eCRF.

Administration of BC-819: Study treatment will be administered as described in Section 9.4 of the protocol. The window for treatment administration should be ± 5 days during induction and ±1 week during maintenance. However, treatment is not to be more frequent than every 5 days at any time during study.

13. STATISTICAL METHODS PLANNED AND SAMPLE SIZE

13.1 Determination of Sample Size

The primary endpoint of the study will be based on patients in the full analysis set (FAS) population. The primary endpoint will be analyzed using a two-sided 95% CI for the CR rate in patients who have CIS at baseline (with or without papillary disease). A total of 140 treated patients will be included in this study, and it is estimated that between 70 and 100 of these will have CIS. Assuming at least 70 patients with CIS, this sample size will provide over 95% power to detect a difference in CR rate in CIS patients of 20% and an alternative hypothesis rate of 40% using an exact binomial test with a nominal 0.05 two-sided significance level. If 100 CIS patients are treated, the power will be approximately 92% to detect a difference from 20% using an alternative hypothesis rate of 35%. The power is higher to detect differences from rates lower than 20%.

13.2 Patient Populations

FAS: All patients who are enrolled in the study (ie, signed the ICF) and received at least 1 dose of study medication. This population will be used for efficacy and safety analyses.

A per-protocol efficacy analysis may be conducted based on patients who met all requirements for the target disease at study entry and received all the prescribed treatment without major protocol violations that might have a major effect on efficacy analysis. Classes of major protocol deviations will be defined and documented prior to the conduct of the primary analysis. These will include but are not limited to significant misuse of the drug (eg, wrong dose, missed doses, too long a delay) and violations of target disease (eg, presence of muscle invasion on subsequent review). This analysis will only be performed if a sizeable number of patients are excluded based on this review. Further detail will be included in the statistical analysis plan.

Any AEs and laboratory data generated prior to start of treatment will be included in separate listings from those of patients treated during the study.

13.3 Subject Disposition

The number of patients who complete and who do not complete the study will be summarized. Reasons for patients not completing the study will be categorized as follows:

- Adverse event:
    - Related to study medication
    - Related to study procedure
    - Unrelated to either study medication or procedure
- For patients with CIS at baseline, failure to clear CIS lesions by the 12-week cystoscopy. These patients can be followed by cystoscopy in the study until they begin an alternative treatment or undergo cystectomy
- Recurrence: recurrence requiring discontinuation from the study (see Section 9.6)
- Death from any cause (with specification of cause of death)
- Withdrawal of consent

- Loss to follow-up
- Other (with specification of reason)

The primary reason for discontinuation will be listed. Thus, if a patient discontinues therapy because of an AE and subsequently dies, the reason for discontinuation will be listed as AE.

As etiology of AEs is often uncertain, more than 1 reason for an AE resulting in discontinuation (eg, both BC-819 and study procedure [catheterization]) may be listed as causes, although the primary reason for discontinuation will be AE.

13.4 Demographics and Baseline Characteristics

Demographic and pre-treatment patient characteristics, including disease parameters and comorbidities, will be summarized with descriptive statistics. The descriptive statistics will include sample size, mean, standard deviation, median, minimum, and maximum for continuous variables and number and percentages for discrete variables. No formal inferential tests will be performed.

13.5 Efficacy Analysis

13.5.1 Primary Efficacy Analysis

The primary endpoint of the study is the CR rate in patients with CIS, supported by duration of the complete response.

A CR in patients with CIS is defined as at least one of the following:

- Negative cystoscopy and negative (including atypical) urine cytology
- Positive cystoscopy with biopsy-proven benign or low-grade NMIBC and negative cytology
- Negative cystoscopy with malignant urine cytology if cancer is found in the upper tract or prostatic urethra and random bladder biopsies are negative

The complete response in patients with CIS for this endpoint must be documented on or after the Week 12 response assessment and on or prior to the Week 48 assessment. The durability of the CRs will be described using Kaplan-Meier Plots of the duration of CR in responders. Duration of complete response in patients with CIS will be calculated from the documented onset of the complete response to the assessment where the patient no longer meets the definition of complete response. More generally, ~~R~~recurrence is defined as the reappearance or persistence of high-grade disease or new high-grade disease. Recurrence must be biopsy proven. Persistence, appearance, or presence of lower grade disease will not be considered recurrence. Sensitivity analyses for duration of response will be performed starting from the time the CIS lesion clears to time that new CIS lesions are identified, censoring patients with no CIS but other high-grade disease at the time of recurrence and a separate analysis looking at the time from response until any NMIBC is found (including low-grade disease).

13.5.2 Interim Analyses

The first 35 patients in the study are to be CIS patients (with or without papillary disease). An interim analysis for futility will be conducted using the response data in these patients. If 9 or fewer of these first 35 patients achieve CR, the study may be stopped for futility. If 10 or more

patients achieve a CR, then the study will continue and all patients meeting entry criteria may be enrolled (including those with papillary disease without CIS). The enrollment will be paused after 35 patients to evaluate this data unless 10 or more responses have already been documented when the 35th CIS patient is enrolled.

When the true CR rate is 40% or higher, the probability of proceeding with 10 or more CRs out of the first 35 patients is over 94%. When the true CR rate is 15% or lower, the probability of 9 or fewer responses is over 97%.

13.5.3 Secondary Efficacy Analyses

The secondary efficacy endpoints include the following:

- The incidence of EFS at 48 weeks, where EFS is defined as high-grade recurrence-free survival (overall population and subgroup of patients with CIS)
- The incidence of EFS at 12, 24, 36, 72, and 96 weeks, where EFS is defined as high-grade recurrence-free survival (overall population and subgroup of patients with CIS)
- Time to recurrence; recurrence is defined as an EFS event
- The incidence of PFS at 48, 72, and 96 weeks as well as time to progression estimated using Kaplan-Meir methods. Progression is defined as the development of T2 or greater disease. Sensitivity analyses will also be performed and will include any of the following as progressions:
    - An increase in stage from Ta or CIS to T1, or
    - Development of T2 or greater, or
    - Lymph node disease, or
    - Distant metastasis
- Overall survival of patients enrolled in the study at 48, 72, and 96 weeks and survival time estimated using Kaplan-Meier methods
- Changes in quality of life over time, as measured by EORTC QLQ-C30 and QLQ-NMIBC24

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, as will patients with CIS at baseline whose CIS lesions have not resolved by the 12-week cystoscopy.

Any patient without tumor in the bladder but presence of tumor in the upper urinary tract will not be classified as failures in these analyses and will continue study participation.

Rates will be summarized using two-sided 95% confidence intervals (using Kaplan-Meier estimates incorporating censoring for PFS and overall survival and both Kaplan-Meir estimates and exact binomial methods for EFS). Time to recurrence and other endpoints will be examined using Kaplan-Meier methods, with plots for the entire patient population, for subgroups of patients with papillary lesions only, and for patients with CIS (with or without papillary lesions). Time 0 is the time of first treatment with BC-819.

Further sensitivity and subgroup analyses will be described in the statistical analysis plan.

13.5.4 Handling of Missing Data

All efforts will be made to avoid missing data. If, however, it does occur, it will be handled as follows:

- If a visit has been missed and cytology results are available at the next visit and no disease is present, then the earlier visit will be counted as absence of disease.
- In addition, the count of absence of disease will be based on visit findings, meaning that if a patient missed a visit and at the next visit he/she experienced a recurrence, the recurrence will be counted only from the day on which evidence was provided.

Patients with CIS lesions that do not resolve by the 12-week cystoscopy will be classified as EFS events. For Kaplan-Meier analyses of EFS, they will be considered to have recurred at 12 weeks.

Any patient without tumor in the bladder but presence of tumor in the upper urinary tract will not be classified as failures in the CR and EFS analyses and will continue study participation.

Additional subgroup analyses may be included in the statistical analysis plan.

13.6 Safety Analysis

Safety will be assessed by evaluation of AEs and clinical laboratory results.

13.6.1 Adverse Events

AEs will be coded to SOC and PT using MedDRA. All AEs occurring after the patient signs the ICF will be recorded, but only those occurring after the start of the study treatment (TEAEs) will be summarized in tables. AEs occurring between signing of the ICF and start of study medication will be included in separate listings from TEAEs.

AEs will be summarized by incidence of AEs (the number of patients reporting at least 1 episode of a specific AE), incidence of AEs by severity within body system, incidence of AEs by attribution within body system, and incidence of AEs causing withdrawal and incidence of SAEs. Regarding severity and attribution summaries, the most extreme outcome (highest severity and closest to study drug-related) will be used for those patients who experience the same AE on more than 1 occasion.

In addition to standard MedDRA SOC and PT tables of AEs, a composite class of urinary tract–related AEs will also be created and the incidence and severity of AEs in this composite class tabulated. SOC and PTs for urinary tract–related AEs are shown in Table 13.1.

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.

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

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'

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.

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.

16. REPORTING AND PUBLICATION

16.1 Confidentiality of Study Data

Any information relating to the study product or the study, including any data and results from the study, will be the exclusive property of the sponsor. The investigator and any other persons involved in the study will protect the confidentiality of this proprietary information belonging to Anchiano Therapeutics Israel Ltd.

16.2 Publication Policy

Anchiano Therapeutics Israel Ltd. agrees to make the report of the multicenter study results available to all study investigators. The Anchiano Therapeutics Israel Ltd. database is the official data record. A paper will be prepared based on the report and published by all investigators as a group, identifying the lead investigator and sponsor. Notwithstanding this, each investigator has the right to publish his/her "contribution to the study" at any relevant venue as long as the sponsor (Anchiano Therapeutics Israel Ltd.) has been notified and received an advance copy within 30 days of the publication for review. Anchiano Therapeutics Israel Ltd. will have 30 days to review any proposed publication of the data for accuracy and proprietary information.

16.3 Study Registration

This study will be registered on www.clinicaltrials.gov or another publicly accessible database before the enrollment of the first patient. Results from the study will be posted on the registry in accordance with local laws and regulations.

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