Statistical Analysis Plan

Sponsor Name: Anchiano Therapeutics Israel Ltd

Protocol Number: BC-819-18-204

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 Version and Date: Version 1.4, 24-Sep-2018

Syneos Health Project Code: 1010798B

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List of Abbreviations and Definition of Terms

Abbreviation or specialist term	Explanation
AE	adverse event
BCG	bacillus Calmette-Guerin
CIS	carcinoma in situ
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DTA	diphtheria toxin A
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFS	event-free survival
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FAS	full analysis set
FDA	US Food and Drug Administration
MedDRA	Medical Dictionary for Regulatory Activities
NMIBC	non-muscle invasive bladder cancer
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
TEAE	treatment-emergent adverse event
TUR	transurethral resection
WBC	white blood cell
WHO	World Health Organization

1. Introduction

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).

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).

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). t 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.

BC-819 has been designed to exploit the specificity of H19 activation to express diphtheria toxin A (DTA) in bladder cancer cells. BC-819 DS is a double-stranded DNA plasmid 4560 base pairs in length. 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.

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. 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.

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 US Food and Drug Administration (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.

2. Study Objectives

2.1 Primary Objectives

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

- The proportion that achieves a CR after treatment with inodiftagene vixteplasmid

2.2 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

3. Study Design

3.1 Overall 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 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 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.

4. Schedule of Assessments

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 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 2 and Table 3.

Table 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

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 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.

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 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	

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.

5. Endpoints

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

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

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. 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.

5.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- The incidence of event-free survival (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-Meier 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.

5.2 Safety Endpoints

The safety endpoint is occurrence of treatment-emergent adverse events (TEAEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, regardless of relationship to study medication.

6. Analysis Populations

The following analysis sets will be evaluated and used for presentation of the data:

Full Analysis Set (FAS)

The FAS will include 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.

Per-Protocol Set

A per-protocol set will include all 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 of a delay) and violations of target disease (eg, presence of muscle invasion on subsequent review). These analyses will only be performed if more than 10% of patients are excluded from the per-protocol set (in either CIS or overall population) respectively based on this review. The group of patients excluded will be documented ahead of the protocol snapshot for the evaluation of the primary analysis.

7. Statistical Methodology

7.1 Statistical and Analytical Considerations

7.1.1 Statistical Methods

Tabulations will be produced for appropriate demographic, baseline, efficacy, and safety parameters. Continuous variables will be summarized by reporting the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category, where the denominator is the number of non-missing values within category at applicable time point (unless otherwise specified). Time-to-event data will be summarized using the Kaplan-Meier method.

Table 4: Results Reporting Precision

Statistics	Degree of Precision
Min, Max	The same number of decimal places as recorded in the raw data.
Mean and Median	One more decimal place than the raw data.
SD	Two more decimal place than the raw data.

By-patient data listings will be produced for data collected through the study (e.g., CRF and lab). In general, the data listings will be sorted by site number concatenated with patient number, visit/collection date and visit/collection time (if applicable). All data listings that contain an evaluation date will contain a relative study day (Study Day). Pre-treatment and on-treatment study days are numbered relative to the day of the first dose of study medication, which is designated as Day 1. The preceding day is Day -1, the day before that is Day -2, etc. Baseline will be defined as the last evaluable/non-missing observation/assessment prior to the first dose of study product on Cycle 1, Day 1.

Adverse events will be graded by the Investigator based on the CTCAE, Version 5.0, and will be coded for summarization using the Medical Dictionary for Regulatory Activities (MedDRA® Version 21.0 or later). Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (September 2017 version or later).

7.1.2 Visit Windows

All data will be tabulated per the evaluation visit as recorded on the eCRF, even if the assessment is outside of the visit window.

7.1.3 Handling of Missing Data

Missing data handling rules for AE relationship to treatment and AE severity will be described in Section 7.4.1.

For efficacy endpoints, 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 cystoscopy 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 1 day.

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.

Complete dates will be imputed from partial dates of adverse events and medications solely for the purpose of defining treatment emergence for adverse events and prior/concomitant status for medications. The imputed dates will not be presented in the listings. Dates will be defined using the hierarchy of derivations below.

Adverse events:

- For onset date:
    - If only the day part of the AE onset date is missing and occurs in the same month and year as the first dose date of study drug, the date of first dose of study drug will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE;
    - If the day and month parts of the AE onset date are missing and occur in the same year as the first dose of study drug, the date of the first dose of study drug will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE;
    - If the AE onset date is completely missing, the date of the first dose of study drug will be used as the onset date of the AE.
- For end date:
    - If only the day part of the AE end date is missing, the last day of the month will be used to complete the end date of the AE;
    - If the day and month parts of the AE end date are missing, December 31st will be used to complete the end date of the AE;
    - If the AE end date is completely missing and the onset date of the AE occurs after the date of the first dose of study drug, the date of last dose plus 30 days will be used as the AE end date. If the AE end date is completely missing and the onset date of the AE occurs prior to the date of the first dose of study drug the date of the first dose of study drug will be used as the AE end date.

Medications:

- For onset date:
    - If only the day part of the medication onset date is missing and occurs in the same month and year as the first dose date of study drug, the date of first dose of study drug will be used as the onset date of the medication. Otherwise, the first day of the month will be used to complete the onset date of the medication;

- If the day and month parts of medication onset date are missing and occur in the same year as the first dose of study drug, the date of the first dose of study drug will be used as the onset date of the medication. Otherwise, January 1st will be used to complete the onset date of the medication;
- If the medication onset date is completely missing, the date of the first dose of study drug will be used as the onset date of the medication.

- For end date:
  - If only the day part of the medication end date is missing, the last day of month will be used to complete the end date of the medication;
  - If the day and month parts of medication end date are missing, December 31st will be used to complete the onset date of the medication;
  - If the medication end date is completely missing and the onset date of the medication occurs after the date of the first dose of study drug, the date of last dose plus 30 days will be used as the medication end date. Otherwise, the date of the first dose of study drug will be used as the medication end date.

The partial dates of medical history and prior treatments (BCG, Bladder cancer, systemic anti-therapy and radiotherapy) will not be imputed as they are already defined as prior to the treatment. No further imputation of partial dates to determine the pre/post treatment status is needed.

7.1.4 Pooling of Investigative Sites

Data from all participating centers will be pooled prior to analysis. It is anticipated that patient accrual will be spread thinly across centers and summaries of data by center would be unlikely to be informative and will not, therefore, be provided. However, a summary of treated patients by site will be produced.

7.1.5 Determination of Sample Size

Efficacy analyses will generally be conducted for all patients in the FAS, or in the case of the primary endpoint of CR rate will be based on all patients in the FAS with CIS at baseline (with or without papillary disease. The primary endpoint will be analyzed using a two-sided 95% CI for the CR rate. 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%.

7.2 Patient Characteristics

7.2.1 Patient Disposition

The number of patients who complete the planned study treatment (through 96 weeks), are ongoing at time of analysis, and do not complete the planned study treatment (through week 96) will be summarized. Reasons for patients not completing the study treatment will be categorized as follows:

- Adverse event:
- For patients with CIS at baseline, failure to clear CIS lesions by the 12-week cystoscopy
- Recurrence: high grade NMIBC recurrence requiring discontinuation from the study

- Death from any cause (with specification of cause of death)
- Withdrawal of consent
- Loss to follow-up
- Sponsor terminated study

Patient disposition will be presented for all patients. Tabulations will include the following:

- Number of patients signed informed consent
- Number (%) of patients not dosed and reasons not being dosed
- Number (%) of patients dosed
    - Number (%) of patients completing the study
    - Number (%) of patents ongoing at the time of the database cutoff date
    - Number (%) of patients who discontinued the study and reason(s) for discontinuation

A listing of patient disposition will be generated. A listing of screen failure patients and the inclusion/exclusion criteria that were not met (i.e. reason for ineligibility) will be generated.

7.2.2 Protocol Deviations

All major protocol deviations will be summarized and listed.

7.2.3 Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics will be presented for patients with CIS and overall in FAS. The following variables will be listed and summarized using both continuous and categorical descriptive statistics:

- Age
- Gender
- Ethnicity
- Race
- ECOG performance status (0, 1, 2)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

7.2.4 Treatment Exposure and Compliance

No dose reduction of BC-819 is planned and no dose adjustments are allowed in the study.

Study drug exposure will be presented cumulatively. The number of instillations received will be summarized using both continuous and categorical descriptive statistics (e.g., mean and frequency). In

addition, the total number of induction instillations received, the total number of maintenance instillations received, the number of patients with at least 1 missed dose (along with the median number and range of the number of missed doses in these patients), and the number of patients with missed dose due to AE will be summarized.

All dosing data will be presented in a data listing.

7.2.5 Prior Cancer Therapies

The following prior therapies will be tabulated

- Time from initial NMIBC diagnosis
- Number of prior BCG induction courses (with or without maintenance courses)
- Number of prior NMIBC occurrences (initial diagnosis + recurrences)
- Number of prior BCG instillations (total)
    - Number of induction instillations of prior BCG
    - Number of maintenance instillations of prior BCG
- Number of prior BCG instillations (most recent course)
    - Number of induction instillations of most recent BCG course
    - Number of maintenance instillations of most recent BCG course
- Other non-BCG prior bladder cancer therapy overall and by type (ie, MMC or gemcitabine)
- Number with prior systemic anti-cancer therapy
- Tumor staging at study entry
    - CIS alone (i.e., not papillary)
    - CIS with any papillary
        - CIS with any HG T1
        - CIS with HG Ta and no HG T1
        - CIS with LG Ta or T1 and no HG T1 or HG Ta
    - HG Papillary alone (i.e., not CIS)
        - Any HG T1
        - HG Ta and no HG T1
- Time from last BCG administration to diagnosis of current recurrence of NMIBC

All collected information for the diagnosis of history of bladder cancer, prior BCG, other prior bladder cancer therapy (non-BCG), prior systemic anti-cancer therapy, prior radiotherapy (related to study indication), and prior surgery (related to study indication) will be provided in by-patient data listings.

7.2.6 Prior and Concomitant Medications

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.

Prior medication is defined as any medication taken prior to the date first dose of study drug. Concomitant medication is defined as any medication taken on or after the date of first dose of study drug. Medications missing both start and stop dates, or having a start date prior to the first dose of study drug and missing the stop date, or having a stop date on or after the last dose of study drug and missing start date will be counted as concomitant.

The partial dates of medications will be imputed using the rule specified in Section 7.1.3. to determine the prior and concomitant status.

Prior and concomitant medications will be coded using the WHO Drug Dictionary, and patient incidence will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term (PT). Patients will be counted only once for each ATC or preferred name in the event that they have multiple records of the same ATC or preferred name in the database.

All prior and concomitant medications will be included in a by-patient data listing.

7.2.7 Medical Histories

Medical history will be coded using MedDRA and will be summarized in frequency tables by System Organ Class (SOC) and PT.

All medical history data will be included in a by-patient data listing.

7.3 Efficacy Analysis

The efficacy endpoints will be analyzed using the FAS.

7.3.1 Primary Efficacy Analysis

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

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 CR in patients with CIS for this endpoint must be documented on or after the Week 12 response assessment. Duration of CR in patients with CIS will be calculated from the documented onset of the CR to the assessment where the patient no longer meets the definition of CR. The durability of the CRs will be described using Kaplan-Meier plots of the duration of CR in responders. A tabular summary will also be created showing the proportion of patients with baseline CIS who are in response at 12, 24, 36, 48, 72 and 96 weeks using Kaplan-Meier estimates incorporating censoring (note that any patient who achieves response within 4 weeks of the planned assessment will be considered to be in response at that assessment, ie, a patient who has CR at 16 weeks will be a responder at 12 weeks). A similar tabular

summary will be created in the subset of patients with CIS who achieve a CR, that remain in response 12, 24, 36, 48, 52, 60, 72 and 84 weeks after the onset of response, for this summary, two methods will be used one which incorporates censoring and a second where patients who leave the study without losing response are considered failures. A by-patient swim lane plot of the time to CR and duration of CR in patients with CIS who respond will also be created. A similar summary will be created for the EFS (in all patients).

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).

A listing of CR rate and duration of response will be provided.

7.3.2 Secondary Efficacy Analyses

The date of first dose, disease recurrence, disease progression, progression, death, last tumor assessment, last contact, EFS days, and PFS days will be reported in a by-patient listing.

7.3.2.1 Event-Free Survival and Time to Recurrence

EFS is defined as the time from first dose of study medication to the first recurrence of disease or death from any cause. Recurrence of disease is defined as

- Appearance of new high-grade disease (ie, new high-grade papillary disease or new CIS) or
- Failure to clear CIS lesions by Week 12 cystoscopy in patients with CIS at baseline

Recurrence must be biopsy proven. Persistence, appearance, or presence of lower grade disease will not be considered recurrence in the primary EFS analyses. Sensitivity analyses will be performed with lower-grade disease also considered an EFS event.

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

Additionally, the overall proportion of patients who have high grade recurrence (and subcategories of persistent CIS, new CIS, new high-grade papillary disease), development of T2 or greater or metastatic disease, cystectomy and death will be summarized for the FAS, and the subgroups with CIS and papillary only disease.

Kaplan-Meier methods will be used to estimate the EFS (ie, percent surviving without a recurrence) and the 95% confidence interval at 12, 24, 36, 48, 72, and 96 weeks in all patients in the FAS and the subgroup of patients with CIS. The median EFS (ie, median time to recurrence) and its 95% confidence interval will also be estimated. Kaplan-Meier plots for EFS will be created.

A sensitivity analysis will also be performed to analyze EFS using binomial methods where patients are considered as being recurrence-free if they have documented recurrence-free survival by the specified time point. Only evaluable patients will be included in the analysis. Patients will be considered evaluable if they have enough follow-up to determine recurrence status at the time point being summarized or if they have discontinued treatment. Exact 95% confidence intervals for EFS will be calculated.

A sensitivity analysis for EFS will be performed where if a patient missed a visit and at the next visit he/she experienced a recurrence, the recurrence will be counted from the day of the missed assessment. An additional sensitivity analysis will be performed where recurrence of any NMIBC, including low-grade disease, is counted as an EFS event.

Time to recurrence is defined as first dose of study medication to the first recurrence of disease. Patients without a recurrence event (including death) will have their event time censored at the last recurrence-free disease assessment. All analyses performed for EFS, including all sensitivity analyses, will be performed for time to recurrence.

7.3.2.2 Progression-Free Survival and Time to Progression

PFS is defined as the time from first dose of study medication to the first observation of disease progression or death. Progression is defined as the development of T2 or greater disease, which includes lymph node disease and distant metastasis.

Kaplan-Meier methods will be used to estimate the PFS (ie, percent surviving without a PFS event) and the 95% confidence interval at 48, 72, and 96 weeks in all patients in the FAS and the subgroup of patients with CIS. The median PFS and its 95% confidence interval will also be estimated. Kaplan-Meier plots for PFS will be created.

A sensitivity analysis of PFS will also be performed, which also includes an increase in stage from Ta or CIS to T1 as a progression event.

Time to progression is defined as first dose of study medication to the first observation of disease progression. Patients without a progression event (including death) will have their event time censored at the last progression-free disease assessment. All analyses performed for PFS, including all sensitivity analyses, will be performed for time to progression.

7.3.2.3 Overall Survival

OS is defined as the time first dose of study medication until death. Kaplan-Meier methods will be used to estimate the OS (ie, percent surviving without death) and the 95% confidence interval at 48, 72, and 96 weeks in all patients in the FAS and the subgroup of patients with CIS. The median OS and its 95% confidence interval will also be estimated. Kaplan-Meier plots for OS will be created.

7.3.2.4 Quality of Life

Quality of life will be assessed using the EORTC QLQ-C30 (a general questionnaire for cancer) and the QLQ-NMIBC24 (a specific questionnaire for NMIBC disease). The questionnaire is administered at baseline (Day 1) and Weeks 21 and 45 prior to any clinical measurements, assessments, evaluations, or procedures being performed.

The QLQ-C30 is composed of both multi-item scales and single-item measures. These include five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Each of the multi-item scales includes a different set of items and no item occurs in more than one scale.

Each scale will be summarized on a 0-100 scale according to the scoring manual (Fayers). For functional scales and the global health status/quality of life scale, a higher score corresponds to greater function or quality of life. For symptom scales, a higher score corresponds to greater symptom burden.

The QLQ-NMIBC24 is composed of both multi-item scales and single-item measures related to NMIBC. These include five multi-item symptom scales (urinary symptoms, malaise, future worries, bloating and flatulence, and male sexual problems), one multi-item functional scale (sexual function) and five single-item measures (intravesical treatment issues, sexual intimacy, risk of contaminating a partner, sexual enjoyment, and female sexual problems).

Each scale in the QLQ-NMIBC24 will be summarized on a 0-100 scale similar to the scoring described for the QLQ-C30 (Fayers; Blazeby). For functional scales (sexual function and sexual enjoyment), a higher score corresponds to greater function or quality of life. For symptom scales, a higher score corresponds to greater symptom burden.

Each scale from the two questionnaires will be summarized descriptively at baseline and the subsequent visits using the actual score at the visit and the change from baseline at the visit. Means, standard deviations, medians, range, and the 95% confidence interval for the mean will be summarized.

7.4 Safety Analysis

Safety will be assessed by evaluation of AEs and clinical laboratory results. All safety analyses will be performed using FAS.

7.4.1 Adverse Events

Adverse events will be graded according to the NCI CTCAE Version 5.0, coded using the MedDRA coding system, and displayed in tables and data listings by system organ class (SOC) and preferred term (PT).

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 and within 30 days of the last administration of study medication or is deemed to be related to study medication. AEs that occur after 30 days of the last administration of study medication and are not related to study medication will not be considered TEAEs.

All AEs occurring after the patient signs the ICF will be recorded, but only the 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.

If the start date of an AE is partially or completely missing, the date will be imputed using the rules specified in Section 7.1.3 to determine the treatment emergence. . The AE will be assumed to be treatment-emergent if it cannot be definitively shown that the AE did not occur or worsen during the treatment-emergent period (worst case approach).

Adverse events are summarized by patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given SOC or PT (i.e., the most related occurrence or the most intense occurrence). Missing relationship will be considered definitely related to BC-819.

An overall AE incidence summary table will be produced and will include:

- The number and percentage of patients reporting at least 1 TEAE
- The number and percentage of patients reporting at least 1 serious AE (SAE)
- The number and percentage of patients reporting at least 1 TEAE with toxicity grade of 3 or higher
- The number and percentage of patients reporting a TEAE leading to withdrawal of study drug

- The number and percentage of patients reporting a TEAE leading to study drug interruption
- The number and percentage of patients reporting a TEAE leading to death
- The number and percentage of patients reporting at least 1 TEAE related to treatment
- The number and percentage of patients reporting at least 1 treatment-related TEAE with toxicity grade of 3 or higher
- The number and percentage of patients reporting at least 1 treatment-related serious AE (SAE)
- The number and percentage of patients reporting a treatment-related TEAE leading to death

Tabulations by SOC and PT will be produced for all TEAEs, treatment-related TEAEs, SAEs, treatment-related SAEs, TEAEs Grade ≥3 (including columns for highest grade 3, 4, and 5), treatment-related TEAEs Grade ≥3 (including columns for highest grade 3, 4, and 5),TEAEs leading to study drug withdrawal, TEAEs leading to study drug interruption, treatment-related TEAEs leading to death and TEAEs, treatment-related TEAEs and SAEs by maximum toxicity grade. These will be presented by SOC and PT, sorted by decreasing frequency. The tabulations will be also be presented separately by PT, sort by decreasing frequency. All tabulations will be presented by overall patients. Additionally, overall summary, TEAEs, treatment-related TEAEs, TEAEs Grade ≥3, treatment-related TEAEs Grade ≥3, SAE, treatment-related SAE, treatment-related death will also be tabulated by patients with baseline CIS.

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 4.

Table 4 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

No formal hypothesis-testing analysis of AE incidence rates will be performed. All AEs occurring on-study will be provided in data listings. By-patient listings also will be provided for the following: SAEs, AEs leading to study drug withdrawal, and AEs leading to study drug interruption.

7.4.2 Physical Examination

Physical examinations will be performed at the time points specified in

Table 1, Table 2, and Table 3. Findings will be listed.

7.4.3 Vital Signs

Vital signs will be performed at the time points specified in

Table 1, Table 2, and Table 3. The actual value and change from baseline to each visit and at end of study will be descriptively summarized by visit/assessment for vital signs (i.e., systolic and diastolic blood pressure, pulse rate, respiratory rate, temperature, and body weight).

Height is measured at screening only. All vital sign data will be reported in a by-patient listing.

7.4.4 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.

Electrocardiogram data will be provided in a by-patient listing.

7.4.5 Laboratory Parameters

Safety laboratory assessments will be performed at the time points specified in

Table 1, Table 2, and Table 3.

The actual value and change from baseline to each visit and at end of study for each laboratory parameter reported in Table 5 will be descriptively summarized. Shift from baseline to highest CTCAE grade tables for key parameter will also be presented. The number and percentage of patients with any laboratory CTCAE grade increase from baseline and a laboratory CTCAE grade increase from baseline to Grade 3-4 will be summarized.

Laboratory results will be included in by-patient listings.

Table 5 Clinical Laboratory Parameters

Hematology	Chemistry	Urinalysis
Hemoglobin	Albumin	Blood
Total red blood cell count	Alkaline phosphatase	Leukocytes
Total white blood cell (WBC) count	Aspartate aminotransferase	Glucose
absolute values for individual WBC types	Alanine aminotransferase	Ketones
Platelets	Bicarbonate	Nitrites
	Bilirubin	pH
	Blood urea nitrogen	Protein
	Calcium	Specific gravity
	Chloride	Microscopic: WBC, red blood cells, bacteria, epithelial cells, crystals (with type identified), and mucus
	Creatinine	
	Glucose	
	Potassium	
	Sodium	
	Total protein	

7.4.6 Evaluation of Performance Status

The frequency distribution of Eastern Cooperative Oncology Group (ECOG) performance status will be collected at screening and at each study visit in conjunction with the physical examination. ECOG performance assessments will be summarized and listed.

Table 6 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

7.5 Interim Analysis

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%.

The interim analysis will include summaries of patient disposition, demographics, baseline characteristics, study drug exposure, efficacy and safety data. The summary of efficacy data will include the analysis of the primary endpoint described in Section 7.3.1. This includes a summary of the CR rate, duration of response, and a swim-lane plot. The summary of safety data will include the analyses specified in Section 7.4.1 for TEAEs, treatment-related TEAEs, SAEs, treatment-related SAEs, TEAEs Grade ≥3, and treatment-related TEAEs Grade ≥3 by SOC and PT and by PT alone.

The TLF shells of the interim analysis will be provided in the appendix.

7.6 Subgroup Analysis

For efficacy, subgroup analyses will be performed for the CR rate, duration of response, and EFS rate at 48 weeks. The EFS rate at 48 weeks will be based on Kaplan-Meier methods. Subgroup analyses will be performed for the following pre-planned subgroups:

- Tumor staging (CIS alone, CIS with any papillary, HG papillary without CIS [EFS only])
- ECOG 0-1 vs 2
- Recurrence ≤ 6 months from last BCG vs > 6 months
- Age (≥65 vs <65)
- Gender
- Race (only if there are more than 10 patients of non-White race)
- BCG unresponsive at most recent recurrence vs. not

Subgroup analyses for the CR rate will be conducted in patients with CIS at baseline, while subgroup analyses for duration of response will be conducted in patients with CIS at baseline with a CR. Subgroup analyses for EFS will be performed for patients in the FAS.

For the key safety analysis (TEAE, treatment-related TEAE, SAE, treatment-related SAE, TEAEs Grade ≥3, and treatment-related TEAEs Grade ≥3) the analysis will be performed by below planned subgroups:

- Age (≥65 vs <65)
- Gender

- Race

7.7 Changes to Methods Planned in the Protocol

There are no changes from the analysis planned in the protocol.

8. Tables, Listings, And Figures

8.1 Programming Guidelines

Computer-generated output will adhere to the following specifications. The standard operating procedures (SOPs) of Syneos Health Clinical will be followed in the creation and quality control of all tables, listings and figures.

8.1.1 Format of Output

Unless otherwise specified, all computer-generated output should be produced in landscape mode. Required margins: at least 1.25 inches on top (the binding margin [or left for portrait output]), at least 1 inch on right, left, and bottom. All output should have the Sponsor name, protocol number, the type of delivery, and page number. Tables/listings/figures should be internally paginated in relation to total length (i.e., page number should appear sequentially as page n of N, where N is the total number of pages in the table). All output should have the following header at the top of the page:

Sponsor Name Protocol XXXXXXX	Confidential	Page n of N

1. Output numeration will conform to International Conference on Harmonization (ICH) recommendations. The study population should be identified immediately following the title.
2. Column headings should be in initial upper-case characters.
3. For numeric variables, include “unit” in column or row headings where appropriate.
4. Footnotes should be single spaced, but separated by at least a double space from the bottom line of the table. The notes are aligned vertically by the left vertical border of the table.
5. If the categories are not ordered (e.g., race), then only those categories for which there is at least 1 patient represented in 1 or more groups should be included.
6. An Unknown or Missing category should be added to any parameter for which information is not available for 1 or more patients.
7. Listings should be sorted by dose levels and patient numbers.
8. In a listing, display the patient number only once for the patient with multiple records. If a patient’s records run into multiple pages, display the patient number once for every page.

8.1.2 Format of Data

1. Unless otherwise specified for continuous variables, the estimated mean, SD and median for a set of values should be printed out to 1 more significant digit than the individual units of measurement. The minimum and maximum should report the same significant digits as the original values.
2. Data in columns of a table should be formatted as follows:
   - Alphanumeric values are left-justified.
   - Whole numbers (e.g., counts) are right-justified.

- Numbers containing fractional portions are decimal aligned.

3. Unless otherwise specified, percentage values should be printed with 1 digit to the right of the decimal point (e.g., 12.8%, 5.4%). Less-than signs "<0.1%" should be printed when values are >0.0 and <0.1% (not 0.0%).

4. Missing data should be represented on patient listings as either a hyphen ("-") with a corresponding footnote (" - = unknown or not evaluated"), or as "N/A," with the footnote "N/A = not applicable," whichever is appropriate.

5. Dates should be printed in SAS ISO 8601 format ("YYYY-MM-DD": 2000-JUL-01). Missing portions of dates should be represented on patient listings as missing (2000-JUL). Dates that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

6. Time should be printed in SAS TIME5.format ("HH:MM": 17:30). Missing portions of time should be represented on patient listings as dashes (--:30). Times that are missing because they are not applicable for the patient are output as "N/A", unless otherwise specified.

8.2 Table of Contents for Tables, Listings and Figures

8.2.1 List of Tables

To be provided with TLF Shells

8.2.2 List of Listings

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9. References

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10. Appendices

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