Cover Page for Study Protocol

Sponsor name	Sesen Bio, Inc.*
NCT Number	NCT02449239
Sponsor trial ID:	VB4-845-02-IIIA
Official title of study	Open-Label, Multicenter, Ph 3 [Phase 3] Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects With Non Muscle-Invasive Carcinoma in Situ and/or High-Grade Papillary Disease of the Bladder Treated With BCG
Document Date	26 January 2017

*Note: Sponsor subsequently underwent a name change (from Eleven Biotherapeutics, Inc. to Sesen Bio, Inc.) but the protocol was not amended with the new Sponsor name

Version Number	Summary of Changes
4.0	• Updated Sponsor name from Viventia Bio, Inc. to Eleven Biotherapeutics, Inc. • Updated exploratory endpoints - added inclusion of biomarker status from positive bladder biopsies, added provision for additional PK sampling in the event of renal or hepatic AEs • Added additional clarification on timing for prior adequate BCG status • Exclusion criteria modified to include: subjects with T1 disease may have CT urogram or MRI urogram with or without (if indicated) contrast, subjects with UTI requiring antibiotic may defer treatment start until resolution of UTI, added allowance for patients with low-risk prostate cancer • Hematology/Chemistry added requirement for chemistry labs during induction phase: drawn one day prior to dosing and results reviewed prior to dosing for weeks 1-6 and drawn within 3 days of last dose and within 4 days of current week's dose and reviewed prior to dosing for weeks 7-12; added requirement to draw chemistry labs withing 5 days of dosing and to review the results prior to dosing during maintenance phase • Added Vicinium holding criteria for serum creatinine, creatinine clearance, AST, ALT levels, clinically significant UTI requiring antibiotics • Added clarification regarding the adverse event handling of pre-existing medical conditions • Added request for additional biopsy slides for potential evaluation of additional biomarkers

Version Number	Summary of Changes
3.0	• Revised the patient population to include three cohorts and modified the primary and secondary endpoints to reflect this revision • Added week 12 assessment of anti-Vicinium antibodies and modified the maintenance anti-Vicinium antibody target collection to a window encompassing weeks 23-27 • Added second restaging biopsy for subjects with T1 and clarified the requirements • Specified that only most recent biopsy needs to occur within 8-week screening window • Modified definition of women of childbearing potential and added requirements for contraception use • Added inclusion criterion of Karnofsky performance status ≥60 and removed life expectancy of at least 4 years • Clarified prior BCG to accurately define adequate BCG • Revised QTc cutoff of >470 to apply to all subjects and added details on conduct of assessments and allowances for known or suspected causes of QTc prolongation. • Modified the inclusion criteria limits for creatinine and creatinine clearance • Changed overall timing for study from months-based to weeks-based • Changed Inclusion Criterion 2 timing of recurrence from 6 months to 26 weeks ±2 weeks • Changed timing for upper tract radiological imaging from 6 months to 26 weeks • Added clarification on requirement for random biopsies • Added information for a consent form for potential subjects to have their biopsy samples sent for central pathology review prior to signing the full study ICF • Changed prostatic urethral biopsy from required to recommended for all male subjects with CIS. • Changed timing wherein upper tract radiological imaging is required from within 6 months before start of dosing to within 13 weeks before start of dosing. • Increased chemistry lab testing to weekly in the Induction Phase and every-other-week in the Maintenance Phase • Changed physical examination from every 6 months to a targeted physical examination every 4 weeks • Updated timing for post-treatment evaluations from within 2 weeks to 30-37 days after last dose • Minor edits, typos and formatting corrections for consistency and clarity

Version Number	Summary of Changes
2.0	• Removed presence of upper tract disease in the absence of disease in the urinary bladder as part of the complete response definition • Added Event-free survival as a secondary endpoint and minor formatting of the Safety and tolerability of Vicinium therapy endpoint • Specified inclusion of subjects with any grade T1 disease • Removed the requirement for biopsy (directed and random) upon completion of the induction phase and at the 12-month time point during Maintenance • Removed random biopsy as a requirement when not indicated • Added that bladder biopsy must confirm diagnosis within 8 weeks of initiating study drug • Added that bladder biopsy must confirm diagnosis within 8 weeks of initiating study drug • Added evidence of higher stage disease by pelvic imaging to exclusion criteria • Complete response rate updated to only include subjects with CIS with or without papillary disease • Removal of prespecified efficacy threshold and update of censoring and event rules of EFS • Removed presence of upper tract disease in the absence of disease in the urinary bladder as part of the complete response definition • Clarified the definitions for treatment failure with respect to low-grade Ta and low-grade T1 recurrence • Added the requirement for Complete Blood Count prior to the second of the twice weekly doses during weeks 2-6 of induction, pre-dose during weeks 7-12 of induction, and monthly during maintenance dosing • Removed Month 12 (Primary Endpoint Evaluation) • Added requirement for subject to be in the supine position when vital signs are measured • The statement defining success as an exclusion of a 20% complete response rate by the lower limit confidence interval at 18 months was removed.

CLINICAL STUDY PROTOCOL

An Open-Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects with Non Muscle-Invasive Carcinoma in Situ (CIS) and/or High-Grade Papillary Disease of the Bladder Previously Treated with Bacillus Calmette-Guérin (BCG)

Protocol Number	VB4-845-02-IIIA
Study Drug	Oportuzumab Monatox (Vicinium™)
IND Number	100,408
Date of Original Protocol	April 3, 2015
Date of Amendment(s)	September 8, 2015 June 22, 2016: Incorporates Clarification Letters 1, 2, and 3 and Administrative Letter 1 January 26, 2017: Incorporates Administrative Letters 2 and 3
Development Phase	3
Sponsor	Eleven Biotherapeutics, Inc 3711 Market Street, 8th Floor Philadelphia, PA 19104 147 Hamelin Street Winnipeg, MB R3T 3Z1 Telephone: 204-478-1023

CONFIDENTIALITY STATEMENT

1 PROTOCOL SIGNATURE PAGE

Sponsor Approval:

_____
Medical Monitor Name and Title (print)

_____ _____
Medical Monitor Signature Date

[redacted] _____ _____
Date
Chief Medical Officer
Eleven Biotherapeutics, Inc.

2 PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Telephone Number	Email Address
24-hr Primary Emergency Medical Contact	[redacted]	[redacted]	[redacted]
24-hr Secondary Emergency Medical Contact	[redacted]	[redacted]	[redacted]
24-hr SERIOUS ADVERSE EVENT Reporting	[redacted]	[redacted]	[redacted]

3 INVESTIGATOR'S PROTOCOL AGREEMENT

PROTOCOL NUMBER: VB4-845-02-IIIA

PROTOCOL TITLE: An Open-Label, Multicenter Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects with Non Muscle-Invasive Carcinoma in Situ (CIS) and/or High-Grade Papillary Disease of the Bladder Previously Treated with Bacillus Calmette-Guérin (BCG)

Protocol Amendment 3 Issue Date: 26 January 2017

I have read the attached protocol and agree that it contains all the necessary details for performing the study. I confirm that I will conduct this study as outlined in the protocol and in conformance with the principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and in accordance with Food and Drug Administration (FDA) regulations and guidelines.

I understand that all information supplied to me by Eleven Biotherapeutics Inc. in connection with this study and not previously published, is confidential information. I hereby assure that no information based on the conduct of this study will be released without prior consent from Eleven Biotherapeutics Inc. unless this requirement is superseded by regulatory authorities.

I understand that I must obtain written informed consent from each participant or their legal representative prior to any study procedures being performed.

I understand that I must obtain Institutional Review Board (IRB) approval of the informed consent, protocol, any amendments, and periodic re-approval as required.

I confirm that I will report all adverse events (AEs) and serious AEs, in accordance with this protocol.

I assure access by Eleven Biotherapeutics Inc., its representatives or monitors to original source documents.

I confirm that I am informed of the need for record retention and that no data can be destroyed without the written consent of Eleven Biotherapeutics Inc.

I confirm that the subjects to whom the drug will be administered will be under the Investigator's personal supervision or under the supervision of an Investigator responsible to that Investigator.

I confirm that study drug will not be supplied to any other Investigator that is not a sub-investigator per the 1572. Supplying study drug to a satellite site requires Sponsor approval.

By my signature below, I hereby attest that I have read, understood, and agree to abide by all conditions, instructions, and restrictions contained in the protocol.

Investigator's signature:_____ Date: _____

Investigator's name (printed): _____

4 LIST OF ABBREVIATIONS

Table 2: Abbreviations

Abbreviation	Explanation
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BCG	bacillus Calmette-Guérin
BIW	twice weekly
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CIS	carcinoma in situ
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
DoR	duration of response
DSMB	data safety monitoring board
ECG	electrocardiogram
EOS	end-of-study
EpCAM	epithelial cell adhesion molecule
ETA	exotoxin A
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	investigational new drug application
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mITT	modified intent-to-treat
mL	milliliter
msec	milliseconds
NCI	National Cancer Institute
NMIBC	non-muscle invasive bladder cancer
OS	overall survival
PFS	progression-free survival

Abbreviation	**Explanation**
QTc	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
Ta	non-invasive papillary carcinoma
Tis	carcinoma in situ
T1	tumor invades lamina propria
T2	tumor invades muscularis propria
TCC	transitional cell carcinoma
TEAE	treatment-emergent adverse event
TTP	time to progression
TURBT	transurethral resection of bladder tumor(s)
ULN	upper limit of normal
UTI	urinary tract infection
WBC	white blood cell

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6 SYNOPSIS

Name of Sponsor/Company: Eleven Biotherapeutics, Inc.

Name of Investigational Product: Vicinium™

Name of Active Ingredient: Oportuzumab monatox

Title of Study: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects with Non Muscle-Invasive Carcinoma in Situ (CIS) and/or High-Grade Papillary Disease of the Bladder Previously Treated with Bacillus Calmette-Guérin (BCG)

Study center(s): Approximately 75

Study period:	**Phase of development:** 3
Estimated date first subject enrolled: August 2015 Estimated date last subject completed: August 2018	

Objective(s):

To assess the efficacy and tolerability of Vicinium when administered as a monotherapy intravesical instillation in subjects with non muscle-invasive bladder cancer - CIS, high-grade Ta or any grade T1 papillary disease or CIS plus papillary disease - who failed previous treatment (i.e., not those who are intolerant) with BCG.

Endpoints:

Primary: Complete response rate in subjects with CIS (with or without papillary disease) whose disease is refractory or relapsed in 6 months or less following adequate BCG treatment

Duration of response (DoR) will be estimated (Kaplan-Meier Estimate) for those subjects with CIS (with or without papillary disease) who experience a complete response.

Secondary:

- Complete response rate and DoR in subjects with CIS (with or without papillary disease) whose disease is refractory or relapsed from 6 months to 11 months following adequate BCG treatment
- Complete response rate and DoR in all subjects with CIS (with or without papillary disease) following adequate BCG treatment
- Event-free survival (EFS) in all subjects
- Complete response rate in subjects at 3, 6, 9, 12, 15, 18, 21, and 24 months in subjects with CIS
- Time to cystectomy in all subjects
- Time to disease recurrence in all subjects
- Progression-free survival (PFS) in all subjects
- Overall survival (OS) in all subjects
- Safety and tolerability of Vicinium therapy in all subjects

Exploratory:

To evaluate biomarkers that may be associated with response or disease progression or treatment failure, which may include, for example, EpCAM status, tumor subtype morphology, furin levels in tumor cell endosomes, presence of a glycosaminoglycan coat, and presence of receptors that could impede a host anti-tumor immune response such as PD-L1.

Methodology: This is an open-label, non-randomized, multicenter study in approximately 134 adults with non-muscle invasive bladder cancer (NMIBC). All subjects must have received "adequate BCG treatment" defined as at least 2 courses of full dose BCG, i.e., at least one induction course of at least 5 doses given within 7 weeks, and a second course (maintenance or second induction) of at least 2 doses given within 6 weeks. Full-dose BCG is:

- TICE® BCG: one vial of TICE containing 1 to 8 x 10^8 colony-forming units (CFU) equivalent to approximately 50 mg (wet weight)
- ImmuCyst® BCG: one vial of ImmuCyst containing 81 mg (dry weight) equivalent to approximately 10.5 ± 8.7 x 10^8 CFU

or equivalent.

The "5+2" doses must be given within approximately 1 year (i.e., the start of one course to start of the second course within 12 months ±1 month) and given to treat the same disease episode with which the subject is enrolling. Additional doses and courses of BCG are permitted as part of "adequate BCG." All subjects must have disease for which the investigator would not treat with additional BCG treatment at this time.

Three cohorts of subjects will enroll:

- Cohort 1: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.
- Cohort 2: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed more than 6 months but within 11 months of the last dose of adequate BCG treatment.
- Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.

For eligibility and cohort assignment, 6 months is defined as 30 weeks, i.e., 26 weeks (6 months) plus an additional 4 weeks to accommodate scheduling variations and for diagnostic work-up, and 11 months is defined as 50 weeks, i.e., 48 weeks (11 months) plus an additional 2 weeks to accommodate scheduling variations and for diagnostic work-up.

Of the 134 subjects ≥77 subjects will accrue to Cohort 1. Up to 57 additional subjects in total may accrue to Cohorts 2 and 3. This is an outpatient study. All treatments may be administered in the study clinic. Each subject's study course consists of a Screening Period, a 12-week Induction Phase, a Maintenance Phase and a Post-Treatment Evaluation. Following the 12-week Induction Phase, subjects will be evaluated for disease status as described in **Section 14**. Subjects without a treatment failure as specifically defined in **Section 14.2** or other criteria necessitating discontinuation of study treatment (see **Section 11.3)** will begin the Maintenance Phase. Subjects will receive treatment for up to 2 years in total if they are tolerating treatment and do not meet the definition of protocol-defined treatment failure or other criteria for study discontinuation. Following the Post-Treatment Evaluation, additional subject data will be collected as needed for the evaluation of the Secondary Endpoints.

The treatments are as follows:

Induction Phase (Weeks 1-12)	30 mg of Vicinium in 50 mL of saline administered intravesically twice weekly (BIW) for 6 weeks followed by once weekly for 6 weeks, for a total of 12 weeks. The twice-weekly doses are to be administered at least 48 hours apart (and no more than 2 doses may be administered within a calendar week, i.e., within a Sunday through Saturday period.) As an example, while a Monday/Thursday or Tuesday/Friday would be optimal, a Monday/Wednesday, Tuesday/Thursday or Wednesday/Friday dosing schedule could be used. There will be a total of 18 doses over the 12-week period of the Induction Phase.
Maintenance Phase (up to Week 104)	30 mg of Vicinium in 50 mL of saline administered intravesically once every other week.

Screening/Baseline: Informed consent, indicated by the subject signing the ICF, must be obtained before any screening assessments or procedures are performed that are solely for determining study eligibility. Assessments and procedures performed as routine care or standard of care before the subject signs the ICF may be utilized to determine eligibility if these are performed within the study-specified time intervals. Screening procedures will include medical history, cystoscopy, urine cytology, directed biopsy, physical examination, 12-lead electrocardiogram (ECG), vital signs, and clinical laboratory analyses. Also, all female subjects of childbearing potential will take a urine or serum pregnancy test. Screening procedures are to be completed within the 8 weeks prior to the initial dose of study drug.

Drug Administration: Subjects will be asked to refrain from fluid intake 2 hours prior to and during the 2-hour period that study drug is held in the bladder to reduce urine flow during the instillation and dwell of Vicinium.

Immediately prior to bladder catheter insertion, subjects will empty their bladder. Appropriate study personnel will then insert a bladder catheter, and the bladder will be drained.

Vicinium 30 mg in 50 mL of saline will be administered intravesically through the catheter. After complete administration of the Vicinium dose, the catheter may be clamped and remain in for the 2-hour dwell time, or it may be removed, per the discretion of the investigator. Subjects will be instructed to hold the study drug in the bladder for 2 hours. During this time, subjects will be required to the best of their ability, to position themselves upright (standing or sitting), prone, supine, and in the left and right lateral decubitus positions for at least 15 minutes each, in any order. After 2 hours, the bladder will be drained and the catheter removed (if the catheter remained in place) or the subject will void to empty their bladder. The subject must remain at the clinic for the entire 2 hour dwell duration.

An appropriate local anesthetic and sterile lubricant may be used at the time of catheterization. In addition, an antibiotic may be given at the discretion of the Investigator.

Study Procedures: At each dosing visit, pre-dose and post-dose, vital sign measurements and adverse event assessments will be conducted. At the Screening cystoscopic assessment, visual mapping and recording of the position of tumors in the bladder must be performed, including quantification of the overall area of the bladder affected. Directed biopsies will be performed prior to the first dose to histologically confirm non-muscle invasive bladder cancer. Urine cytology will be performed prior to the last dose in the Induction Phase, and cystoscopy will be performed at the end of the Induction Phase. Cystoscopy and cytology will also be assessed every 13 weeks (3 months) during the Maintenance Phase. At each cystoscopic evaluation while the subject is on-study, directed biopsies should be taken from all areas of apparent disease or suspicious for disease, including any area of inflammation. When positive or suspicious cytology is observed in the case of negative cystoscopy, random bladder biopsies will be obtained from the locations of disease identified at Screening (i.e., by screening biopsies and the screening bladder mapping) and from other areas of the bladder so that all the following areas of the

bladder have been biopsied: the dome, the posterior wall, the left and right lateral walls, the trigone and the bladder neck, and in males, the prostatic urethra. Blood will be drawn at Baseline, during week 12 and after approximately 6 months of therapy for determination of plasma anti-Vicinium antibodies. Blood will be drawn on Day 1 pre-dose and at the end of the 2-hour dwell time, and at the end of the 2-hour dwell time in Week 6 (12th treatment) and Week 12 for the determination of Vicinium plasma levels.
Periodic clinical lab tests and pregnancy tests (in females) will be performed.

Additional study procedures will include triplicate ECGs for QTc analysis at completion of the Induction Phase and EpCAM determination by immunohistochemistry on all positive biopsies.

Post-Treatment Evaluation: Subjects will return for Post-Treatment evaluations between 30 and 37 days after their last dose of study treatment. Post-treatment procedures include cystoscopy, directed biopsy and urine cytology (if the subject has not discontinued protocol therapy due to disease recurrence or progression and if these evaluations have not been performed in the prior 8 weeks), as well as safety assessments of vital signs, triplicate ECG, physical examination, clinical laboratory analyses, and adverse events and concomitant medications assessments. If a cystoscopy is required, it should be performed as soon as possible on or after Day 30 post-treatment.

Number of subjects (planned): Approximately 134 subjects. ≥77 subjects will enroll in Cohort 1. Up to 57 subjects will enroll in Cohort 2 and Cohort 3 combined.

Criteria for inclusion/exclusion:

Inclusion

A subject will be eligible for inclusion in this study if all the following criteria apply:

1. Histologically-confirmed non muscle-invasive urothelial carcinoma (transitional cell carcinoma) of the bladder as follows:
   - CIS (with or without papillary disease) OR
   - Any grade T1 papillary disease OR
   - High-grade Ta papillary disease

   based on a biopsy within 8 weeks of the initial dose of study treatment. If multiple bladder biopsies are required to confirm eligibility, the last bladder biopsy to the initial dose of study treatment must be within 8 weeks. This diagnosis must be confirmed by the independent central pathology reviewer prior to subject enrollment.

   A subject with persistent T1 disease on the second (i.e., restaging) TURBT (see **Section 10.1**) may be enrolled in this study only if the investigator documents the subject declines cystectomy.

2. Subjects must have received adequate BCG treatment defined as at least 2 courses of BCG, i.e., at least one induction and one maintenance course or at least 2 induction courses. The initial induction course must be at least 5 treatments within a 7-week period. The second course (induction or maintenance) must be at least 2 treatments within a 6-week period. The "5+2" doses of BCG must be given within approximately 1 year (i.e., the start of one course to start of the second course within 12 months ±1 month) and for the same disease episode for which the subject is enrolling. Treatment must be considered "full-dose" BCG (see **Section 10**). If additional doses or courses of BCG above the minimum "5+2" are given, these do not have to be within the same approximate 12-month timeframe.

   Subjects who were unable to receive at least 5 doses of BCG in a first course and at least 2 doses of BCG in a second course due to intolerance are not eligible.

   Subjects who began their initial course of BCG with "full-dose" BCG and required dose-reductions due to adverse events but are still able to tolerate at least "5+2" doses of BCG are considered to meet the requirement for "adequate BCG." Subjects who received less than "full

dose" BCG (e.g., 1/3rd dosing) as a standard regimen and not due to dose reductions because of AEs are not eligible.

The BCG may have been given in combination with interferon. When BCG is given simultaneously in combination with interferon, 1/3rd dosing of BCG is acceptable.

3. The subject's disease is refractory or has relapsed following adequate BCG treatment. Refractory disease is defined as disease which persists at the first evaluation following adequate BCG. Relapsed disease is defined as having a complete response to adequate BCG but recurs at a subsequent evaluation.

   Subjects will enroll into one of three cohorts based on their type of disease and the time to refractory/relapsed disease following their last dose of BCG as follows:

   - Cohort 1: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.
   - Cohort 2: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed more than 6 months but within 11 months of the last dose of adequate BCG treatment.
   - Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.

   For eligibility and cohort assignment, 6 months is defined as 30 weeks i.e., 26 weeks (6 months) plus an additional 4 weeks to accommodate scheduling variations and for diagnostic work-up and 11 months is defined as 50 weeks i.e., 48 weeks (11 months) plus an additional 2 weeks to accommodate scheduling variations and for diagnostic work-up.

   For subjects enrolling in Cohort 2: The investigator documents he/she would not treat the subject with additional BCG at the time of study entry.

4. Male or non-pregnant, non-breastfeeding female, age 18 years or older at date of consent.
5. All women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days of the first dose of study therapy. A woman is not of childbearing potential if she has undergone surgical sterilization (bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) or if she is ≥55 years of age and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for at least 12 months and there is no other cause of amenorrhea (e.g., hormonal therapy, prior chemotherapy).
6. All sexually active subjects agree to use barrier contraception (i.e., condoms) while receiving study treatment and for 120 days following their last dose of study treatment. WOCBP and males whose sexual partners are WOCBP agree to use barrier contraception and a second form of contraception while receiving study treatment and for 120 days following their last dose of study treatment.
7. Karnofsky performance status ≥ 60 (**Appendix 1**).
8. Adequate organ function, as defined by the following criteria:
   - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x upper limit of normal (ULN);

- Total serum bilirubin ≤1.5 x ULN (CTCAE Grade ≤ 1);
- Serum creatinine ≤ 1.5 x ULN; or a creatinine clearance ≥40 mL/min;
- Hemoglobin ≥8.0 g/dL;
- Absolute neutrophil count ≥1500/mm^3;
- Platelets ≥75,000/mm^3.

9. Ability to understand and sign an Independent Ethics Committee- or Institutional Review Board-approved informed consent document indicating that the subject (or legally acceptable representative) has been informed of all aspects of the trial and is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. The informed consent document must be signed prior to the subject undergoing tests or procedures solely for determining study eligibility and prior to receiving any protocol treatment.

Exclusion

A subject will not be eligible for this study if any one or more of the following criteria apply:

1. The subject is pregnant or breastfeeding.
2. Evidence of urethral or upper tract transitional cell carcinoma (TCC) within the past 2 years.

   Subjects with T1 disease must have no evidence of upper or lower tract disease or a more advanced stage of disease by CT urogram or MRI urogram of the abdomen and pelvis performed within 8 weeks of the first dose of study treatment. If intravenous contrast is contraindicated, retrograde ureteropyelography, or CT or MRI without intravenous contrast may be performed.
3. Subjects with hydronephrosis, except for those subjects where hydronephrosis has been longstanding (i.e., predates the diagnosis of the CIS, Ta or T1 by more than 2 years) and diagnostic evaluation at Screening shows no evidence of tumor. Subjects with hydronephrosis that is unequivocally unrelated to upper tract malignancy may be considered eligible with Sponsor approval.
4. Any intravesicular or other chemotherapy treatment within 2 weeks or any investigational agent within 4 weeks prior to the initial dose of study drug.
5. History of recurrent severe urinary tract infections (UTIs) per investigator judgment. Subjects with a current UTI requiring antibiotic treatment may defer the initiation of Vicinium treatment on Day 1 until resolution of the UTI (even if this extends the screening period requirements to start of Vicinium treatment).
6. Active, uncontrolled impairment of the urogenital, renal, hepatobiliary, cardiovascular, gastrointestinal, neurologic or hematopoietic systems which, in the opinion of the Investigator, would predispose the subject to the development of complications from the administration of intravesical therapy and/or general anesthesia.
7. The subject has a diagnosis of another malignancy within 2 years before the first dose of study treatment, except for superficial skin cancer or localized solid tumors deemed cured by surgery and not treated with systemic anticancer therapy and not expected to require anticancer therapy in the next 2 years i.e., while the subject may be taking study treatment. However, subjects with low-risk prostate cancer, e.g.:

   - Clinically localized disease (≤T2a) and

- Gleason score 6 (3+3) and
- Serum PSA <10 ng/mL

undergoing active surveillance may be enrolled with agreement of the sponsor.

8. A QTc interval of >470 msec by the Fridericia formula (QTcF), at the Screening ECG. If the subject's QTcF is >470 msec on the initial ECG, a total of 3 ECGs should be obtained at least 3 minutes apart and all within 30 minutes. The average of the 3 QTcF's will be used to determine eligibility. Known or suspected causes of prolonged QTc can be treated (e.g., hypocalcemia, hypokalemia, hypomagnesimia) and the ECGs may be repeated. If the subject initiates treatment with a drug known to prolong the QTc during the Screening period after the initial Screening ECGs were obtained, the Screening ECGs must be repeated once the new drug has reached steady state to ensure the average QTcF remains ≤470 msec. For subject's whose heart rate is <60 bpm, the Bazett correction formula (QTcB) may be used.
9. Subjects who, in the opinion of the Investigator, cannot tolerate intravesical administration or intravesical surgical manipulation (cystoscopy, biopsy) due to the presence of serious comorbid condition(s) (e.g., uncontrolled cardiac or respiratory disorders).
10. Local or severe allergy to any components of the drug regimen.

Investigational product, dosage and mode of administration: Vicinium™ 30 mg in 50 mL of saline administered intravesically

Duration of treatment: Up to 24 months

Reference therapy, dosage and mode of administration: None

Criteria for evaluation:

Efficacy: Efficacy assessments will consist of cystoscopy, urine cytology, and cystoscopic bladder biopsies. These measurements will be at scheduled intervals throughout the trial and at the Post-Treatment evaluation.

Safety: The following safety data will be collected during the study: adverse events (including serious adverse events), clinical laboratory blood and urine tests, vital signs, triplicate ECGs, and physical examinations.

Statistical methods:

Sample Size: Assuming the true complete response rate is 30%, sample sizes associated with various widths of a two-sided, exact (Clopper-Pearson) 95% confidence intervals are provided in the table below:

Sample Size (N)	**Target Distance from P to Lower Limit**	**Proportion (P)**	**Lower Limit**
121	0.080	0.300	0.220
95	0.090	0.300	0.210
76	0.100	0.300	0.200

The primary efficacy analysis will be based on the complete response (CR) rate and duration of response in subjects in Cohort 1. Under the provided assumptions, a sample size of 77 evaluable subjects in Cohort 1 is sufficient to estimate complete response rate with an exact 95% confidence interval that excludes 0.2 (PASS 2008).

The total sample size of 134 subjects (i.e., those with CIS (with or without papillary disease) and those with papillary-only disease) will provide at least 80% power to test the null hypothesis that the event-free survival rate at 18 months is 20% versus the alternative hypothesis that the event-free survival rate at 18 months is ≥30%. This calculation is based on the assumptions of a nonparametric distribution for event-free survival and the length of follow-up is 24 months.

Efficacy Analysis: The number and percentage of subjects with CIS with or without papillary disease with a complete response will be summarized separately at each assessment. Ninety-five percent (95%) confidence intervals around the complete response rate will be calculated using the Clopper-Pearson method. For subjects with CIS with or without papillary disease who achieve complete response, the duration of response, defined as the start of the complete response to documented treatment failure (**Section 14.2**) or death as a first event, will be estimated using the method of Kaplan-Meier. Any subject who does not experience treatment failure, disease progression or death will be censored at the last non-missing assessment.

Event-free survival will be estimated using the method of Kaplan-Meier and will include all enrolled subjects i.e., those with CIS (with or without papillary disease) and those with only papillary disease (see **Section 14.3** for events included in this analysis). Subjects who do not experience an event will be censored at the last non-missing assessment. Subjects with persistent or recurrent disease at their first response evaluation will be treated as having an event at Day 1. The ninety-five percent (95%) confidence interval around the event-free survival rate at 18 months will be presented. Analyses of other time-to-event efficacy endpoints (time to cystectomy, time to progression, progression-free survival, and overall survival) will be analyzed in a similar manner.

Safety Analysis: Adverse events will be summarized by treatment, system organ class and preferred term. Tabulations and listings of values for ECGs, vital signs and clinical laboratory tests will be presented. Any abnormal or out-of-range values from clinical laboratory tests or physical examinations will be presented in data listings.

7 INTRODUCTION

Bladder cancer is the 6th most common cancer in the United States, affecting more men than women. It is the 3rd most common cancer in men and the 11th most common in women. (Bladder cancer treatment (PDQ®) 2015) Approximately 75% of bladder cancers are of the non-muscle invasive type. (Babjuk 2013) Non-muscle invasive bladder cancers (NMIBCs) can be categorized as Ta (non-invasive papillary carcinoma), T1 (tumor invades lamina propria or subepithelial connective tissue), and Tis (carcinoma *in situ*). Ta tumors are the most common, representing about 70% of NMIBCs, but only about 7% of these are categorized as high-grade. (Sylvester 2005) About 20% of NMIBCs are T1 tumors. (Anastasiadis 2012) T1 tumors are more aggressive than Ta tumors, and considered high-risk. (Babjuk 2013, American Urological Association 2014) Flat, high-grade tumors confined to the mucosa (non-invasive) are characterized as carcinoma *in situ* (CIS), (Babjuk 2013) and these represent approximately 10% of the NMIBCs. (Anastasiadis 2012)

The usual first treatment for NMIBC (Ta, T1, and CIS) is transurethral resection of the bladder tumors (TURBT), followed by intravesical immunotherapy, most commonly with bacillus Calmette-Guérin (BCG). (Babjuk 2013, American Urological Association 2014) In patients with T1 tumors, a second TURBT is recommended. (Babjuk 2013, American Urological Association 2014) Induction therapy with BCG is usually dosed as 6 once-weekly instillations. (Babjuk 2013, American Urological Association 2014) In patients with high-grade Ta, T1, and CIS, maintenance therapy with BCG of at least 1 year is recommended, (Babjuk 2013, Anastasiadis 2012) although the optimal dose, dosing schedule, and duration of treatment are unknown. (American Urological Association 2014). Local and systemic side effects are common with intravesical BCG therapy, causing discontinuation of treatment in approximately 20% of patients. (Sylvester 2011) Approximately 75% of patients experience local side effects (including cystitis, irritative voiding symptoms, and hematuria), while 40% report systemic side effects, including general malaise and fever. (Sylvester 2011) Intravesical BCG failure occurs in up to 40% of patients. (Sylvester 2011) Because of the high risk for development of muscle invasive disease, cystectomy is recommended for CIS and high-grade Ta and T1 patients who experience disease recurrence following intravesical therapy. (Babjuk, 2013, American Urological Association 2014) For patients unable or unwilling to undergo cystectomy, treatment options are limited.

Vicinium™ (Vicinium) contains the active pharmaceutical ingredient VB4-845, which is a recombinant fusion protein produced in *Escherichia coli* (*E. coli*) that expresses a humanized single-chain antibody fragment (scFv) specific for the epithelial cell adhesion molecule (EpCAM) antigen linked to ETA(252-608). ETA(252-608), which is a truncated form of *Pseudomonas* exotoxin A (ETA) that lacks the cell binding domain, is a single polypeptide fusion protein produced by continuous translation of a single construct.

The mechanism of action is dependent upon the 2 components of Vicinium. Once bound to the EpCAM antigen on the surface of carcinoma cells, Vicinium is internalized through an endocytic pathway. Furin contained within the endosomal compartment cleaves a proteolytic site on the surface of ETA(252-608), releasing ETA(252-608). The ETA(252-608) induces cell death by irreversibly blocking protein synthesis through adenosine diphosphate (ADP)-ribosylation of a post-translationally modified histidine residue of elongation factor-2 (EF-2), called diphthamide. (Oppenheimer 1981) The truncated version of ETA, ETA(252-608), has been engineered to retain the active domains necessary to induce cell death, but the cell binding domain has been eliminated

thereby preventing the ETA(252-608) moiety from entering the cell in the absence of some alternate vehicle, such as *via* antibody-mediated internalization. Binding to EpCAM must occur to result in ETA(252-608)-mediated effects.

The ETA(252-608) component of the Vicinium fusion protein can cause an immunogenic response when administered systemically to humans. Therefore, Vicinium is being developed as a locally targeted therapeutic in order to limit its systemic exposure and to maximize the concentration of the drug in its target cells. By administering Vicinium *via* intravesical instillation, the probability of systemic exposure and subsequent generation of neutralizing antibodies is decreased. Furthermore, the high local concentrations of Vicinium maximize the likelihood of achieving a therapeutic benefit.

Preclinical Studies

Preclinical study data have shown that Vicinium exhibits potent activity [inhibitory concentration 50% (IC_{50}) = 0.001 - 10 pM] against numerous EpCAM-positive cell lines, with selectivity for EpCAM-expressing tumors. *In vivo* pharmacology demonstrated that Vicinium effectively inhibits tumor growth in several human xenograft animal models. Studies in rats found that the toxicological effects of Vicinium occur at doses 1,000-fold greater than the IC_{50} for activity on tumor cells, with a safety margin of at least 5- to 100-fold.

Clinical Studies

A Phase 1 trial (VB4-845-02-I) of Vicinium evaluated doses up to 30.16 mg administered intravesically to 64 subjects with Grade 2 or 3, stage Ta or T1 transitional cell carcinoma (TCC) or CIS, either refractory to or intolerant of BCG therapy (Kowalski 2010). No dose-limiting toxicities (DLTs) were observed. Vicinium was well tolerated, and the majority of adverse events (AEs) were mild. The most frequently reported treatment-related AEs were renal and urinary disorders, with dysuria (14.1%) and hematuria (10.9%) most commonly reported. Of the systemic AEs, fatigue was reported by 7.8% of subjects, while fever/chills and loss of appetite were each reported by 6.2% of subjects. The frequency of treatment-related AEs did not increase with increasing doses of Vicinium. There was 1 serious adverse event reported (death due to cardiac failure), which occurred 3 weeks after stopping study drug; the Investigator assessed the event to be unrelated to Vicinium treatment, attributing it to the subject's long-standing history of cardiovascular disease. Exploratory efficacy assessment at 3 months showed that of 61 evaluable subjects, a complete response (defined as non-positive urinary cytology and either normal cystoscopy or abnormal cystoscopy with negative biopsy) was achieved by 24 subjects (39%). Of the 17 subjects with Tis, 29% achieved a complete response, while non-recurrence at 3 months was observed in 44% and 43% of the subjects with T1 and Ta, respectively. Blood samples for pharmacokinetic analysis were taken on day 1 prior to and 1, 2, and 3 hours post-dosing. Pre-dose samples were also taken on days 8, 15, 22, 29, and 36. Post-instillation plasma levels of Vicinium were measured in 63 patients, except at the final visit where samples were provided by 61 patients. In almost all patients, Vicinium plasma levels were below the limit of detection of the assay (14 pg/mL) at all time points examined. VB4-845 was detectable in only two patients: one had levels of 19 and 17 pg/mL at 1 hour after Vicinium instillation and on day 8 prior to dosing, respectively, and the other had a level of 18 pg/mL at the 1 hour time point.

Blood samples for assessing humoral immune reactivity to Vicinium were taken prior to dosing on days 1, 8, 15, 22, 29, 36, and at the final study visit. Antibody titers to the scFv and ETA252–608 portions of the fusion protein (human antihuman antibodies (HAHA) and human anti-Pseudomonas antibodies (HAPA)) were measured using an enzyme-linked immunosorbent assay. HAPA response was more vigorous, as patients developed a measurable titer earlier; the majority of patients

exhibited HAPA by day 29, with 77% (47/61) having a measurable titer at final visit. In contrast, only 16% (10/61) of patients had HAHA by the end of the study. HAPA titers were also generally higher, with a mean maximum titer of 20,512 versus 3373 for HAHA responses. A comparison of mean titers of the HAPA and HAHA responses measured in samples taken on the final visit showed no significant difference between responders and nonresponders.

A Phase 2 study (VB4-845-02-IIA) evaluated once-weekly instillations of Vicinium 30 mg in two different induction schedules: weekly x 6 weeks or weekly x 12 weeks, followed by up to 3 maintenance cycles (3 once-weekly instillations followed by a 9-week drug-free period) in 46 subjects with histologically-confirmed TCC of the bladder and residual CIS with or without concurrent Ta or T1 who were refractory or intolerant to BCG. (Kowalski 2012). Some subjects in the 6-weekly induction arm received a second induction cycle. Forty-five subjects were considered evaluable for response. A complete response (defined as no histological evidence of disease and negative urine cytology at the 3-monthly evaluations) was achieved by 44% (20/45) of subjects, and 16% (7/45) of subjects remained disease-free at the 1-year end-of-study (EOS) assessment. A post-study assessment found that these subjects were still disease-free at 18-25 months. The median time to recurrence was 134 days longer in subjects who received 12 weeks of induction therapy compared to 6 weeks (408 vs 274 days, respectively; log rank test p=0.1708). The most frequently reported treatment-related AEs were renal and urinary disorders, including 50% with dysuria (61% of these were of mild intensity) and 13% with hematuria. Overall, most AEs were of mild severity. There were 3 severe events, all of which resolved without sequelae. No subject discontinued from the study due to AEs and there were no deaths or other serious AEs.

Based on the preliminary positive therapeutic results and favorable tolerability profile, the present Phase 3 trial will evaluate the efficacy of Vicinium induction therapy administered for 12 weeks, and the long-term effectiveness of Vicinium maintenance therapy (up to 24 months treatment in total) in preventing disease recurrence.

8 PURPOSE

To assess the efficacy and tolerability of Vicinium monotherapy (administered via intravesical instillation) for the treatment of non muscle-invasive bladder cancer - CIS, high-grade Ta or any grade T1 papillary disease or CIS plus papillary disease in subjects who failed previous treatment (i.e., not those who are intolerant) with BCG.

9 STUDY OBJECTIVES

To assess the efficacy and tolerability of Vicinium when administered as a monotherapy intravesical instillation in subjects with non muscle-invasive bladder cancer - CIS, high-grade Ta or any grade T1 papillary disease or CIS plus papillary disease who failed previous treatment (i.e., not those who are intolerant) with BCG.

9.1 Primary Endpoint

Complete response rate in subjects with CIS (with or without resected papillary disease) whose disease is refractory or relapsed in 6 months or less following adequate BCG treatment (see **Section 17.5**).

Duration of response (DoR) will be estimated (Kaplan-Meier Estimate) for those subjects with CIS (with or without resected papillary disease) who experience a complete response.

9.2 Secondary Endpoints

- Complete response rate and DoR in subjects with CIS (with or without papillary disease) whose disease is refractory or relapsed from 6 months to 11 months following adequate BCG treatment
- Complete response rate and DoR in all subjects with CIS (with or without papillary disease) following adequate BCG treatment
- Event-free survival (EFS) in all subjects.
- Complete response rate in subjects after 3, 6, 9, 12, 15, 18, 21, and 24 months in subjects with CIS.
- Time to cystectomy in all subjects.
- Time to disease recurrence in all subjects.
- Progression-free survival (PFS) in all subjects.
- Overall survival (OS) in all subjects.
- Safety and tolerability of Vicinium therapy in all subjects.

9.3 Exploratory Endpoints

To evaluate biomarkers that may be associated with response or disease progression or treatment failure which may include for example, EpCAM status, tumor subtype morphology, furin levels in tumor cell endosomes, presence of a glycosaminoglycan coat and presence of receptors that could impede a host anti-tumor immune response such as PD-L1.

10 STUDY DESIGN

This is an open-label, non-randomized, multicenter, multiple-dose, study of Vicinium in approximately 134 subjects with histologically-confirmed non muscle-invasive carcinoma in situ (CIS) and/or papillary disease (high grade Ta or any grade T1) of the bladder who failed previous treatment (i.e., not those who are intolerant) with BCG.

All subjects must have received "adequate BCG treatment" defined as at least 2 courses of full dose BCG i.e., at least one induction course of at least 5 doses given within 7 weeks, and a second course (maintenance or second induction) of at least 2 doses given within 6 weeks. Full dose BCG is

- TICE® BCG: one vial of TICE containing 1 to 8 x 10^8 colony-forming units (CFU) equivalent to approximately 50 mg (wet weight)
- ImmuCyst® BCG: one vial of ImmuCyst containing 81 mg (dry weight) equivalent to approximately 10.5 ± 8.7 x 10^8 CFU

or equivalent.

The "5+2" doses must be given within approximately 1 year (i.e., start of one course to the start of a second course within 12 months ±1 month) and given to treat the same disease episode with which the subject is enrolling. Additional doses and courses of BCG are permitted as part of "adequate

BCG." All subjects must have disease for which the investigator would not treat with additional BCG at this time.

Three cohorts of subjects will enroll:

- Cohort 1: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.
- Cohort 2: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed more than 6 months but within 11 months of the last dose of adequate BCG treatment.
- Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.

For eligibility and cohort assignment 6 months is defined as 30 weeks i.e., 26 weeks (6 months) plus an additional 4 weeks to accommodate scheduling variations and for diagnostic work-up and 11 months is defined as 50 weeks i.e., 48 weeks (11 months) plus an additional 2 weeks to accommodate scheduling variations and for diagnostic work-up.

Of the 134 subjects, ≥77 will accrue to Cohort 1. Up to 57 additional subjects in total may accrue to Cohorts 2 and 3. This is an outpatient study. All treatments may be administered in the study clinic.

All diagnostic pathology (bladder tissue and urine cytologies and if performed, tissue from prostatic urethral biopsies) will be reviewed and graded by an independent pathologist and cytopathologist with experience in NMIBC diagnoses. The details of sample handling and logistics will be provided in a separate laboratory manual.

The sample used for determining subject eligibility for inclusion into the trial (post-BCG biopsy) must be reviewed and signed off by the pathologist prior to study enrollment and start of study treatment. All other samples will be read in a timely fashion and the results will be available to study investigators via the electronic CRF.

Time points for this study will use a week–day convention. For each subject, Day 1 is defined as the date that the subject first receives study drug and will designated as Week 1 Day 1 (W1D1). The day before this date is Day −1 (W−1D−1; there is no Day 0).

Each subject's study course consists of a Screening Period, a 12-week Induction Phase, a Maintenance Phase and a Post-Treatment Evaluation. Subjects will receive intravesical Vicinium instillations twice weekly (BIW) for 6 weeks followed by once weekly for 6 weeks for a total of 18 doses in the Induction Phase. The twice-weekly doses are to be administered at least 48 hours apart (and no more than 2 doses may be administered within a calendar week, i.e., within a Sunday through Saturday). During the Maintenance Phase, Vicinium is administered once every other week. Total duration of treatment (combined Induction and Maintenance Phases) is up to 2 years (104 weeks). Subjects with a protocol-defined treatment failure (see **Section 14.2**) or other criteria for study drug discontinuation (see **Section 11.3**) will be withdrawn from the study.

Subjects will be evaluated for disease every 13 weeks (**Figure 1**, **Section 10.4**, **Section 10.5**). The first on-study evaluation will occur after the Induction Phase. At Week 12, a urine sample for cytology will be collected. In Week 13, subjects will undergo cystoscopy. Subjects without

treatment failure (see **Section 14.2**) or other criteria necessitating treatment discontinuation (**Section 11.3**) will enter the Maintenance Phase.

Figure 1: Disease Evaluation Schedule

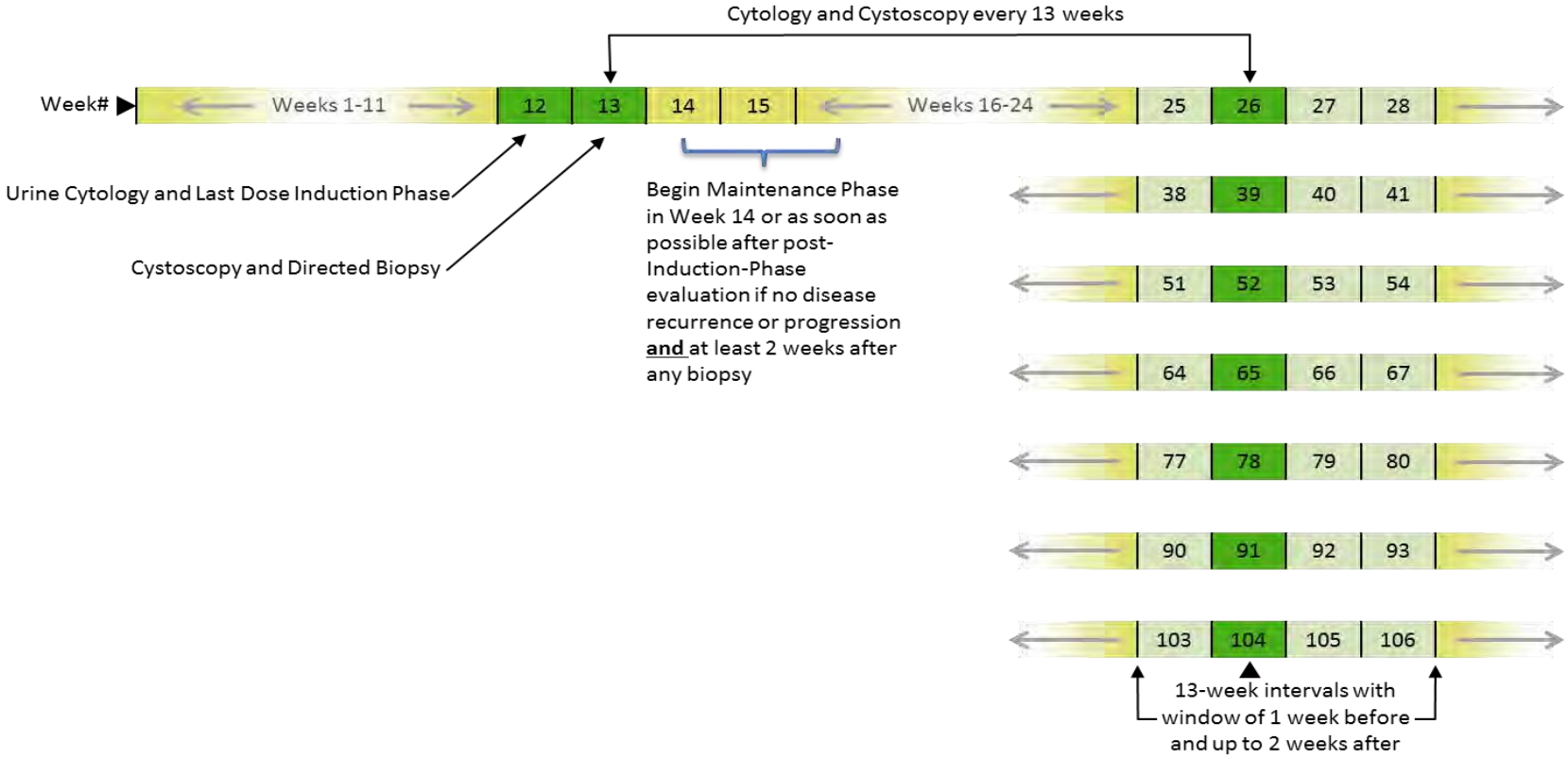
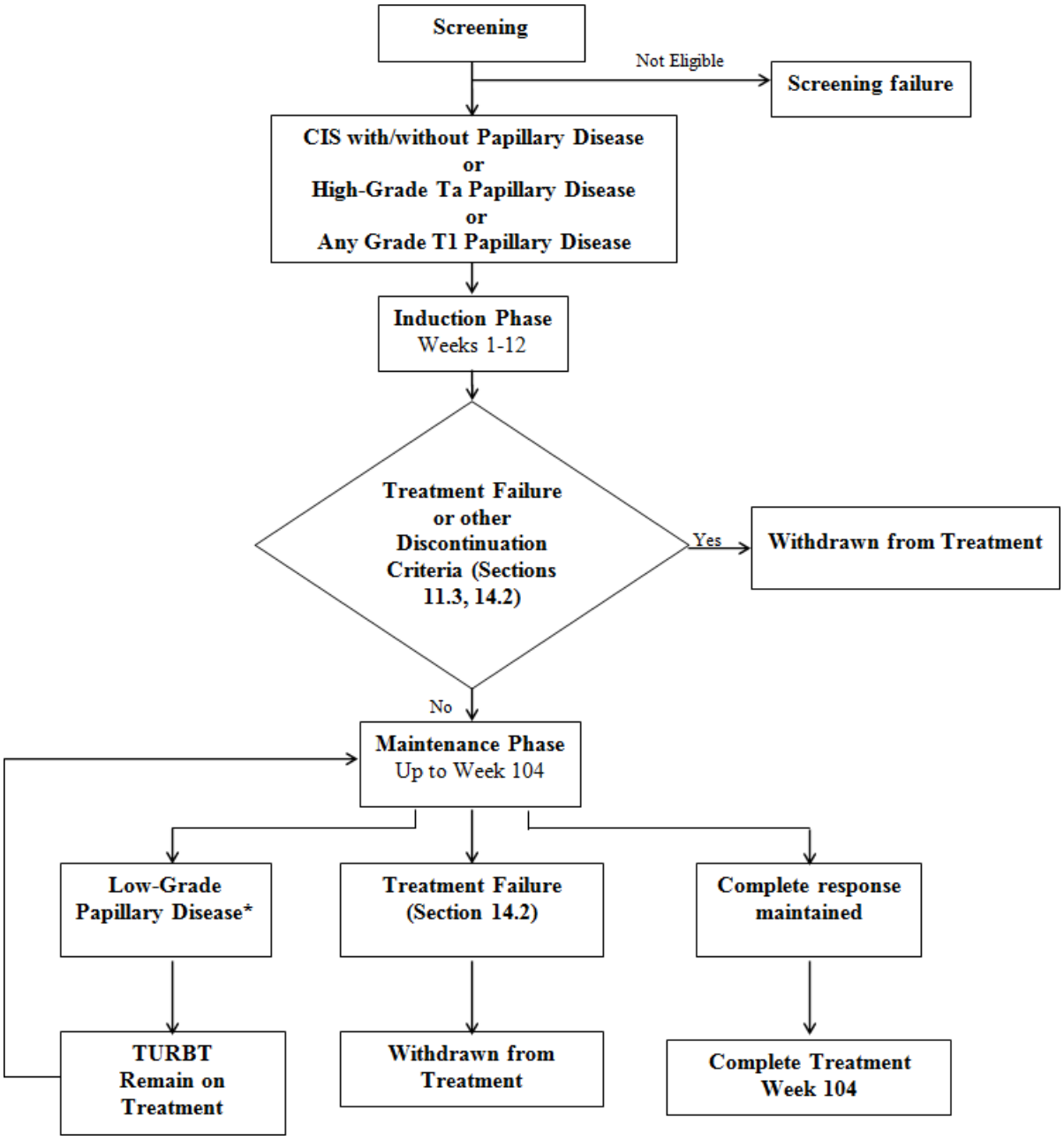


Figure 2: Study Flow Diagram



*Subjects that enter the study with high-grade disease and have documented low-grade disease on study are not considered to have a treatment failure. Subjects who enter with only low-grade T1 disease and who have a recurrence of low-grade T1 disease are considered to have a treatment failure and are withdrawn from further treatment.

10.1 Screening Period (Within 8 Weeks (≤56 Days) Before the First Vicinium Treatment)

Prior to the conduct of any study procedure, signed, written informed consent including HIPAA authorization, if applicable, must be obtained from all potential subjects.

Informed consent must be obtained before a subject undergoes any study-specific tests or procedures, i.e., test or procedures that would not be done as part of routine or standard of care but are being performed only for study purposes (i.e., solely to determine eligibility).

If a patient has had bladder biopsy with or without any other urinary tract biopsy performed (e.g., prostatic urethral biopsy) within the past 8 weeks as part of routine/standard of care, the patient may be asked to sign a pathology evaluation consent form prior to signing the full informed consent form to give permission for their biopsy samples to be sent for central pathology review to determine if the patient would be eligible for the study based on their current disease histology.

Once consent is obtained, subjects will be assigned a subject number (**Section 18.1**) and the following assessments and procedures are to be completed within the 8 weeks before the first dose of Vicinium:

- Review of inclusion and exclusion criteria
- Assess and record dates and doses of prior BCG therapy
- Cystoscopy and Biopsies
    - Standard white-light cystoscopy is to be performed. Fluorescence cystoscopy (e.g., blue light cystoscopy) is acceptable but not required. If a subject undergoes fluorescence cystoscopy for biopsy or TURBT during the screening period, this modality should be used for on-study biopsies or TURBTs. However, white-light cystoscopy is appropriate for routine follow-up assessments if a biopsy is not required.
    - Directed biopsies are performed on any area of apparent disease, suspicious disease, or inflammation. If multiple biopsies or TURBTs are required to determine eligibility, the last biopsy or TURBT that confirms eligibility must be within the 8-week screening period. Prior biopsies may be more than 8 weeks before the first dose of Vicinium.
    - For subjects with any papillary disease: All papillary disease must be completely resected e.g., by TURBT, in the screening period.
    - For subjects with T1 disease: the base of the tumor bed must be adequately biopsied so that the sample includes muscle from the base of the lesion(s) in order to demonstrate an absence of muscle invasion. All subjects with T1 disease must undergo a second resection (i.e., restaging TURBT) approximately 2 - 6 weeks after the initial TURBT. Postoperative intravesical chemotherapy (e.g., mitomycin) is acceptable per investigator discretion but cannot be given within 2 weeks of the first dose of Vicinium. For subjects with T1 disease who undergo a restaging TURBT, Vicinium treatment must start within 6 weeks of the restaging TURBT or the last biopsy/TURBT that determines eligibility.
    - **NOTE**: **Subjects should not receive Vicinium treatment within 2 weeks of any biopsy/TURBT in order to permit bladder healing**

- Additional resections or restaging TURBTs not required by this protocol may also be done at Investigator discretion e.g., for high-grade Ta disease, if this is within acceptable practice standards
- Subjects with T1 disease must also have radiological examination (i.e., CT urogram or MRI urogram) of the abdomen and pelvis to rule out more advanced disease. If intravenous contrast is contraindicated, retrograde ureteropyelography, or CT or MRI without intravenous contrast may be performed.
- Prostatic urethral biopsy (males subjects) is recommended particularly for subjects at higher risk for prostatic urethral involvement per investigator discretion. It is not required.
- Upper tract radiological imaging, i.e.., CT urogram or MRI urogram of the abdomen and pelvis, is required if this has not performed within 13 weeks before start of dosing. If intravenous contrast is contraindicated, retrograde ureteropyelography, or CT or MRI without intravenous contrast may be performed. (Note: imaging during screening is a requirement for all subjects with T1 disease as noted above)
- EpCAM determination by immunohistochemistry will be performed on all positive biopsies (baseline and any post-baseline positive biopsies during the study), but confirmation of this is not required prior to enrollment into the trial or the start of study drug administration Additional unstained slides should be submitted for all positive biopsies for biomarker evaluation (**Section 16.7**)
- Demographics (**Section 16.1**)
- Review of medical history, including relevant past medical conditions including other cancers and surgical procedures (**Section 16.1**)
- Review of medication history (including prescription medications, over-the-counter medications, vitamins, supplements, herbal and homeopathic treatments), including previous anti-tumor treatment(s), and life history of drug allergies and intolerances (**Section 16.1**)
- 12-lead electrocardiogram(s) (ECGs) for QTc analysis (**Section 16.4**). Note: If after the ECG is obtained, the subject begins new medication in the Screening period known to prolong the QT interval, the ECG must be repeated after the new drug reaches steady state and prior to the first dose of study drug.
- Vital signs (**Section 16.5**)

Not all Screening/Baseline procedures need to be performed on the same day.

10.2 Baseline (Within 1 Week (≤ 7 Days) Before the First Vicinium Treatment)

The following assessments and procedures must be conducted within the week before first dose of study drug administration:

- Laboratory assessments (**Section 16.2**)
- Complete physical examination, including height and weight (**Section 16.3**)
- Blood sample for determination of plasma anti-Vicinium antibodies
- Urine or serum pregnancy test (females of childbearing potential only)
- Current medication history including prescription medications, over-the-counter medications, vitamins, supplements, herbal and homeopathic treatments

10.3 Induction Phase

During the 12-week Induction Phase, subject will treated twice weekly for 6 weeks followed by once weekly treatment for 6 weeks

Assessments during the Induction Phase are as follows:

10.3.1 Week 1 (Twice Weekly Dosing)

Assessments during week 1 are as follows:

	Week 1 First Dose		Week 1 Second Dose	
Assessment	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**
Urine Cytology	✓			
Chemistry[1]	✓[1]			
Hematology (CBC and differential)[1]	✓[1]			
Urinalysis[1]	✓[1]			
Plasma Vicinium Level	✓	✓[2]		
Physical Examination[3]	✓[3]			
Vital Signs	✓	✓	✓	✓
Adverse Event Assessment	✓	✓	✓	✓
Concomitant Medications	✓	✓[4]	✓	✓[4]

1 Chemistry, hematology, urinalysis (**Section 16.2**): Required only if not obtained in baseline period (within 7 days for first dose of Vicinium)

2 Obtain at the end of the dwell time as soon as possible after the subject voids (or bladder is drained via catheter)

3 Required only if not obtained in the baseline period (**Section 16.3**)

4 Required only if additional medications (not including Vicinium) were administered during or after the start of the instillation

10.3.2 Weeks 2-5 (Twice Weekly Dosing)

Assessments during weeks 2-5 are as follows:

	Week 2 - 5 First Dose Each Week		Week 2 – 5 Second Dose Each Week	
Assessment	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**
Hematology (CBC and differential)[1]			✓[1]	
Chemistry[1]			✓[1]	
Vital Signs	✓	✓	✓	✓
Adverse Event Assessment	✓	✓	✓	✓
Concomitant Medications	✓	✓[2]	✓	✓[2]
Targeted Physical Examination and Weight	Week 4			
Pregnancy Test[3]	Week 4			

1 Chemistry laboratory tests should be drown up to one day before the 2nd dose of the week and results must be reviewed prior to administration of the 2nd dose of the week. With Sponsor approval, the chemistry laboratory tests may be drawn up to one day before the 1st dose of the week and results must be checked prior to administration of the 1st dose of the week. For extreme logistical/laboratory limitations at the site or undue burden on the subject, the sponsor may approve that labs can be drawn up to 2 days before dosing. Hematology tests should be drawn at the same time as chemistry tests for subject convenience (**Section 16.2**).

2 Required only if additional medications (not including Vicinium) were administered during or after the start of the instillation

3 A pregnancy test (urine or serum) is required in week 4 for all WOCBP

10.3.3 Week 6 (Twice Weekly Dosing)

Assessments during week 6 are as follows:

	Week 6 First Dose		Week 6 Second Dose	
Assessment	**Pre-Dose**	**Post-Dose**	**Pre-Dose**	**Post-Dose**
Chemistry			✓[1]	
Hematology			✓[1]	
Plasma Vicinium Level				✓[2]
Urinalysis			✓[1]	
Vital Signs	✓	✓	✓	✓
Adverse Event Assessment	✓	✓	✓	✓
Concomitant Medications	✓	✓[3]	✓	✓[3]

1 Chemistry laboratory tests should be drown up to one day before the 2nd dose of the week and results must be reviewed prior to administration of the 2nd dose of the week. With Sponsor approval, the chemistry laboratory tests may be drawn up to one day before the 1st dose of the week and results must be checked prior to administration of the 1st dose of the week. For extreme logistical/laboratory limitations at the site or undue burden on the subject, the sponsor may approve that labs can be drawn up to 2 days before dosing. Hematology tests should be drawn at the same time as chemistry tests for subject convenience (**Section 16.2**).

2 Obtain at the end of the dwell time as soon as possible after the subject voids (or drug is drained via catheter)

3 Required only if additional medications (not including Vicinium) were administered during or after the start of the instillation

10.3.4 Weeks 7-11 (Once Weekly Dosing)

Assessments during weeks 7-11 are as follows:

	Week 7-11	
Assessment	**Pre-Dose**	**Post-Dose**
Hematology (CBC and differential)[1]	✓[1]	
Chemistry[1]	✓[1]	
Vital Signs	✓	✓
Adverse Event Assessment	✓	✓
Concomitant Medications	✓	✓[2]
Targeted Physical Examination and Weight	Week 8	
Pregnancy Test[3]	Week 8	

1 Laboratory tests will be drawn at least 3 days after the prior week's dose and within 4 days of the current week's planned Vicinium dose. The results must be reviewed prior to administration of the dose.

2 Required only if additional medications (not including Vicinium) were administered during or after the start of the instillation

3 A pregnancy test (urine or serum) is required in week 8 for all WOCBP

10.3.5 Week 12 (Once Weekly Dosing)

Assessments during week 12 are as follows:

	Week 12	
Assessment	**Pre-Dose**	**Post-Dose**
Urine Cytology	✓	
Urinalysis	✓[1]	
Hematology (CBC and differential)	✓[1]	
Chemistry	✓[1]	
Plasma Vicinium Level (Pharmacokinetics)		✓[2]
Vital Signs	✓	✓
Adverse Event Assessment	✓	✓
Concomitant Medications	✓	✓[3]
Targeted Physical Examination and Weight		✓
Triplicate ECGs		✓
Anti-Vicinium Antibodies	✓	
Pregnancy Test[4]	✓	

1 Chemistry and hematology laboratory tests drawn at least 3 days after the Week 11 dose and within 4 days prior to the Week 12 dose and results must be reviewed prior to administration of the dose (**Section 16.2**).

2 Obtain at the end of the dwell time as soon as possible (i.e., within 30 minutes) after the subject voids (or the bladder is drained via catheter)

3 Required only if additional medications (not including Vicinium) were administered during or after the start of the instillation

4 A pregnancy test (urine or serum) is required in week 12 for all WOCBP

10.4 Post-Induction Phase Evaluation

Subjects will be evaluated for disease status at the end of the Induction Phase. Urine cytology is obtained in week 12 as described above. Starting in week 13 (or as soon as possible after week 12) subjects will undergo cystoscopy and directed biopsies/TURBT of all lesions suspicious for disease. Subjects are eligible to receive Maintenance Phase treatment if they do not have a protocol defined treatment failure (see **Section 14.2**) or other criteria for study drug discontinuation (see **Section 14.3**) and are tolerating treatment.

See **Section 14.4** for criteria to continue treatment.

10.5 Maintenance Phase

Disease evaluation will be performed every 13 weeks regardless of dose interruptions or delays (see **Section 14.4**). Cystoscopy and urine collection for cytology during the Maintenance Phase should be done at Week 26, Week 39, Week 52, Week 65, Week 78, Week 91, and Week 104, even if there are

missed doses or dosing delays. Every effort should be made to stay on this evaluation schedule, however, a window of one week before and up to 2 weeks after these time points is permitted (e.g., the Week 26 cystoscopy and urine for cytology may be performed from Week 25 to Week 28, but as close to week 26 as possible). The complete evaluation to determine disease status (e.g., repeat cytology, cystoscopy and biopsies if required) should be completed as soon as possible following the every 13-week timepoint. Vicinium dosing may continue during these disease evaluations in the Maintenance phase per investigator discretion. Vicinium treatment should not be given within 2 weeks of any biopsy/TURBT.

Other assessments during the Maintenance Phase are as follows:

10.5.1 Treatment Days

	Treatment Days	
Assessment	**Pre-Dose**	**Post-Dose**
Vital Signs	✓	✓
Adverse Event Assessment	✓	✓
Concomitant Medications	✓	✓[1]

1 Required only if additional medications (not including Vicinium) were administered during or after the start of the instillation

10.5.2 Every 2 weeks

- Chemistry (see **Section 16.2**). Sample should be drawn at least 7 days after the prior dose and within 5 days prior to day of next dosing and results must be reviewed prior to dosing.

10.5.3 Every 4 weeks

- Hematology (see **Section 16.2**)
- Urinalysis (see **Section 16.2**)
- Targeted physical examination (**Section 16.3**)
- Weight
- Pregnancy test

10.5.4 Between Week 23 – Week 27

- Plasma sample for anti-Vicinium antibodies

10.6 Post-Treatment Evaluation

Subjects will return to the clinic site for a Post-Treatment evaluation 30 – 37 days after their last dose of study treatment.

The following assessments will be performed at that time

- Targeted physical examination (including weight) (**Section 16.3**)

- Triplicate ECG obtained within 30 minutes of each other at least 3 minutes apart
- Vital signs
- Concomitant medications
- Adverse events, including SAEs
- Collection of clinical laboratory samples: blood samples for hematology and chemistry, urine samples for urinalysis
- Anti-Vicinium antibodies
- Blood or urine pregnancy test (WOCBP)
- The following are to be done if the subject has not discontinued treatment due to documented disease recurrence, progression and if they have not been performed within the past 8 weeks
    - Cystoscopy
    - Biopsy (directed). EpCAM determination by immunohistochemistry will be obtained on all positive biopsies.
    - Urine cytology

As described in **Section 15**, additional follow-up will occur for subjects with ongoing clinically significant AEs (e.g., those leading to study drug discontinuation) or SAEs assessed as related to study drug.

Subjects without a treatment failure (see **Section 14.2**) will continue to undergo evaluations for disease status (urine cytology, cystoscopy, directed biopsies) every 13 weeks until the sooner of a treatment failure or the determination of the 18-month event free survival analysis. Survival data also will be collected on subjects every 13 weeks. Once all subjects are no longer receiving study treatment and the 18-month event-free survival for the study is determined, the study will close and subjects will then be followed by their physician according to standard of care.

Table 3: Visit Schedule and Assessments [Screening & Induction]

Assessment	Screening and Baseline Weeks		Induction Phase Weeks 1- 12					Post-Induction Phase
Week	-8 through -1	-1	1	2-5	6	7-11	12	As soon as possible after Week 12
Informed consent	X							
Inclusion/Exclusion criteria	X							
Cystoscopy	X[1,2]							X[2]
Bladder biopsy/TURBT	X[1]							X[3]
EpCAM determination, Biomarker evaluations[15]	X[15]							X[15]
Urine Cytology			X[8]				X[10]	
Demographics	X							
Medical and medication history (including previous anti-tumor therapy and surgical procedures)	X	X[6]						
Physical examination		X	X[8]	X[11]		X[11]	X[11]	
Weight and height		X[12]		X[12]		X[12]	X[12]	
Radiological imaging	X[4]							
Triplicate ECG	X[5]						X[11]	
Vital signs	X		X[9]	X[9]	X[9]	X[9]	X[9]	
Hematology		X	X[8]	X[11]	X[11]	X[11]	X[11]	
Chemistry		X	X[8]	X[11]	X[11]	X[11]	X[11]	
Urinalysis		X	X[8]		X[11]		X[11]	
Anti-Vicinium antibody test		X					X	
Plasma Vicinium Levels (PK)[14]			X		X		X	
Serum or urine pregnancy test		X[7]		X[7]		X[7]	X	
Concomitant medication			X[10]	X[10]	X[10]	X[10]	X[10]	X
Adverse events (AEs / SAEs)			X[9]	X[9]	X[9]	X[9]	X[9]	X
Drug administration (BIW)[13]			X	X	X			
Drug administration (once/week)						X	X	

[1] Must have documented non-muscle invasive urothelial bladder cancer that is histologically confirmed by the independent central pathology reviewer prior to the first dose of study drug. All papillary disease must be completely resected. In subjects with T1 disease, a second (i.e., restaging) TURBT must be performed approximately 2 - 6 weeks after the first. A biopsy may be more than 8 weeks prior to the first dose of study drug as long as the last biopsy that confirms eligibility is within 8 weeks.

[2] White-light cystoscopy. Any subject who undergoes fluorescence cystoscopy for bladder biopsy/TURBT during the screening period must continue having this modality for all subsequent biopsies (however, white-light cystoscopy will suffice for all assessments if a biopsy is not required (**Section 14**).

[3] Directed biopsies of all areas suspicious for disease. Random biopsies are required if cystoscopy is negative and urine cytology is positive or there are two suspicious cytology results (**Section 14**)

[4] CT urogram or MRI urogram. If intravenous contrast is contraindicated, retrograde ureteropyelography, or CT or MRI without intravenous contrast may be performed. Required during Screening for all subjects with T1 disease. Required for all other subjects if not previously performed within 13 weeks before the start of dosing.

[5] Single tracing only at Screening unless QTc is prolonged (**Section 16.4**); thereafter, triplicate ECGs are to be performed.

[6] Update medication history.

[7] Performed every 4 weeks (i.e., week 4, week 8, week 12, etc.) while on treatment in females of childbearing potential only.

[8] Cytology sample pre-dose on Day 1. Note: Chemistry, hematology (CBC and differential), urinalysis and physical examination need to be performed pre-dose Day 1 only if not performed in the Baseline Period (≤7 days before the first dose of study medication).

[9] Evaluation performed pre-dose and post-dose prior to leaving the clinic.

[10] Evaluation performed pre-dose. Concomitant medications required post-dose only if additional medications (not including Vicinium) were administered during or after the start of the instillation.

[11] Weeks 2-5: Chemistry and hematology (CBC and differential) performed once weekly (**Section 10.3.2**). Week 4: Targeted physical examination. Week 6: Urinalysis performed pre-dose at the second dose of the week; Hematology (CBC and differential) and chemistry (**Section 10.3.3**). Weeks 7-11: Chemistry and hematology (CBC and differential) performed once weekly (**Section 10.3.4**). Week 8: Targeted physical examination. Week 12: Urinalysis performed pre-dose. Hematology (CBC and differential), chemistry(**Section 10.3.5**). Targeted physical examination, and triplicate ECG performed post-dose prior to leaving the clinic.

[12] Height and weight at Baseline. Weight performed Week 4, Week 8 and Week 12.

[13] Twice weekly (BIW) dosing with each dose separated by at least 48 hours (and no more than 2 doses within any calendar week (Sunday through Saturday)). As an example, while a Monday/Thursday or Tuesday/Friday would be optimal, a Monday/Wednesday or Tuesday/Thursday, or Wednesday/Friday dosing schedule could be used.
[14] Levels are to be taken pre-dose of first instillation. Additional sampling is at the end of the dwell time as soon as possible (within 30 minutes) after the subject voids (or bladder is drained via catheter) following the first instillation and after the second of the twice-weekly instillations during Weeks 6 and 12.
[15] For all bladder biopsy/TURBT samples positive for urothelial carcinoma (**Section 16.7**).

Table 4: Visit Schedule and Assessments (Maintenance Phase)

Assessment	Maintenance Phase					Post-Treatment (30 – 37 days after last dose)
	Treatment Days	Every 2 Weeks	Every 4 Weeks	Every 13 Weeks	Between Weeks 23 and 27	
Cytology				X[1,10]		X[1,6]
Cystoscopy				X[1,2,10]		X[2,3,6]
Biopsy/TURBT				X[1,3,10, 13]		X[2,3,6,13]
Physical examination			X[7]			X[7]
Triplicate ECG						X
Vital signs	X[4]					X
Weight			X			X
Anti-Vicinium antibody test					X	X
Chemistry		X[12]				X
Hematology and urinalysis			X[9]			X
Urine or serum pregnancy test			X[5]			X
Concomitant medication	X[4]					X[8]
Adverse events (AEs / SAEs)	X[4]					X
Drug administration (once every other week)	X					
Contact to assess for progression and survival				X[11]		

[1] Window of 1 week before to 2 weeks after to start evaluation
[2] White-light cystoscopy. Any subject who underwent fluorescence cystoscopy for bladder biopsy/TURBT during the screening period must continue having this modality for all subsequent biopsies (however, white-light cystoscopy will suffice for all assessments if a biopsy is not required (**Section 14**).
[3] Directed biopsies of all areas suspicious for disease. Random biopsies are required if cystoscopy is negative and urine cytology is positive or there are two suspicious cytology results (**Section 14**)
[4] Evaluation performed pre-dose and post-dose prior to leaving the clinic. Concomitant medications required post-dose only if additional medications (not including Vicinium) were administered during or after the start of the instillation
[5] Performed every 4 weeks during study participation in females of childbearing potential only.
[6] Evaluations performed if the subject has not discontinued treatment due to documented disease recurrence, progression and if they have not been performed within the past 8 weeks.
[7] Targeted physical examination.
[8] Additional follow-up will occur for subjects with ongoing clinically significant AEs (e.g., those leading to study drug discontinuation) or SAEs assessed as related to study drug.
[9] Urinalysis performed pre-dose if on a treatment day.
[10] Weeks 26, 39, 52, 65, 78, 91, 104
[11] Starting after subject discontinues study drug. Progression will be assessed if the subject did not have disease progression as the reason for discontinuation of study drug and has not had a cystectomy.
[12] **Section 10.5.2**.
[13] EpCAM and biomarker evaluation on all bladder biopsy/TURBT samples positive for urothelial carcinoma (**Section 16.7**).

11 STUDY POPULATION

11.1 Inclusion Criteria

A subject will be eligible for inclusion in this study if all the following criteria apply:

1. Histologically-confirmed non muscle-invasive urothelial carcinoma (transitional cell carcinoma) of the bladder as follows:
   - CIS (with or without papillary disease) OR
   - Any grade T1 papillary disease OR
   - High-grade Ta papillary disease

   based on a biopsy within 8 weeks of the initial dose of study treatment. If multiple bladder biopsies are required to confirm eligibility, the last bladder biopsy to the initial dose of study treatment must be within 8 weeks. This diagnosis must be confirmed by the independent central pathology reviewer prior to subject enrollment.

   A subject with persistent T1 disease on the second (i.e., restaging) TURBT (see **Section 10.1**) may be enrolled in this study only if the investigator documents the subject declines cystectomy.
2. Subjects must have received adequate BCG treatment defined as at least 2 courses of BCG, i.e., at least one induction and one maintenance course or at least 2 induction courses. The initial induction course must be at least 5 treatments within a 7-week period. The second course (induction or maintenance) must be at least 2 treatments within a 6-week period. The "5+2" doses of BCG must be given within approximately 1 year (i.e., the start of one course to start of the second course within 12 months ±1 month) and for the same disease episode for which the subject is enrolling. Treatment must be considered "full-dose" BCG (see **Section 10**). If additional doses or courses of BCG above the minimum "5+2" are given, these do not have to be within the same approximate 12-month timeframe.

   Subjects who were unable to receive at least 5 doses of BCG in a first course and at least 2 doses of BCG in a second course due to intolerance are not eligible.

   Subjects who began their initial course of BCG with "full-dose" BCG and required dose-reductions due to adverse events but are still able to tolerate at least "5+2" doses of BCG are considered to meet the requirement for "adequate BCG." Subjects who received less than "full dose" BCG (e.g., 1/3rd dosing) as a standard regimen and not due to dose reductions because of AEs are not eligible.

   The BCG may have been given in combination with interferon. When BCG is given simultaneously in combination with interferon, 1/3rd dosing of BCG is acceptable.
3. The subject's disease is refractory or has relapsed following adequate BCG treatment. Refractory disease is defined as disease which persists at the first evaluation following adequate BCG. Relapsed disease is defined as having a complete response to adequate BCG but recurs at a subsequent evaluation.

   Subjects will enroll into one of three cohorts based on their type of disease and the time to refractory/relapsed disease following their last dose of BCG as follows:

- Cohort 1: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.
- Cohort 2: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or relapsed more than 6 months but within 11 months of the last dose of adequate BCG treatment.
- Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease is determined to be refractory or relapsed within 6 months of the last dose of adequate BCG treatment.

For eligibility and cohort assignment: 6 months is defined as 30 weeks i.e., 26 weeks (6 months) plus an additional 4 weeks to accommodate scheduling variations and for diagnostic work-up and 11 months is defined as 50 weeks i.e., 48 weeks (11 months) plus an additional 2 weeks to accommodate scheduling variations and for diagnostic work-up.

For subjects enrolling in Cohort 2: The investigator documents he/she would not treat the subject with additional BCG at the time of study entry.

4. Male or non-pregnant, non-breastfeeding female, age 18 years or older at date of consent.
5. All women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days of the first dose of study therapy. A woman is not of childbearing potential if she has undergone surgical sterilization (bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) or if she is ≥55 years of age and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for at least 12 months and there is no other cause of amenorrhea (e.g., hormonal therapy, prior chemotherapy).
6. All sexually active subjects agree to use barrier contraception (i.e., condoms) while receiving study treatment and for 120 days following their last dose of study treatment. WOCBP and males whose sexual partners are WOCBP agree to use barrier contraception and a second form of contraception while receiving study treatment and for 120 days following their last dose of study treatment.
7. Karnofsky performance status ≥ 60 (**Appendix 1**).
8. Adequate organ function, as defined by the following criteria:
    a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x upper limit of normal (ULN);
    b. Total serum bilirubin ≤1.5 x ULN (CTCAE Grade ≤1);
    c. Serum creatinine ≤1.5 x ULN; or a creatinine clearance ≥40 mL/min;
    d. Hemoglobin ≥8.0 g/dL;
    e. Absolute neutrophil count ≥1500/mm^3;
    f. Platelets ≥75,000/mm^3.
9. Ability to understand and sign an Independent Ethics Committee- or Institutional Review Board-approved informed consent document indicating that the subject (or legally acceptable representative) has been informed of all aspects of the trial and is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. The informed consent document must be signed prior to the subject undergoing tests or

procedures solely for determining study eligibility and prior to receiving any protocol treatment.

11.2 Exclusion Criteria

A subject will not be eligible for participation if any one or more of the following criteria apply:

1. The subject is pregnant or breastfeeding.
2. Evidence of urethral or upper tract transitional cell carcinoma (TCC) within the past 2 years.

   Subjects with T1 disease must have no evidence of upper or lower tract disease or a more advanced stage of disease by CT urogram or MRI urogram of the abdomen and pelvis performed within 8 weeks of the first dose of study treatment. If intravenous contrast is contraindicated, retrograde ureteropyelography, or CT or MRI without intravenous contrast may be performed.
3. Subjects with hydronephrosis, except for those subjects where hydronephrosis has been longstanding (i.e., predates the diagnosis of the CIS, Ta or T1 by more than 2 years) and diagnostic evaluation at screening shows no evidence of tumor. Subjects with hydronephrosis that is unequivocally unrelated to upper tract malignancy may be considered eligible with Sponsor approval.
4. Any intravesicular or other chemotherapy treatment within 2 weeks or any investigational agent within 4 weeks prior to the initial dose of study drug.
5. History of recurrent severe urinary tract infections (UTIs) per investigator judgment. Subjects with a current UTI requiring antibiotic treatment may defer the initiation of Vicinium treatment on Day 1 until resolution of the UTI (even if this extends the screening period requirements to start of Vicinium treatment).
6. Active, uncontrolled impairment of the urogenital, renal, hepatobiliary, cardiovascular, gastrointestinal, neurologic or hematopoietic systems which, in the opinion of the Investigator, would predispose the subject to the development of complications from the administration of intravesical therapy and/or general anesthesia.
7. The subject has a diagnosis of another malignancy within 2 years before the first dose of study treatment, except for superficial skin cancer or localized solid tumors deemed cured by surgery and not treated with systemic anticancer therapy and not expected to require anticancer therapy in the next 2 years i.e., while the subject may be taking study treatment. However, subjects with low-risk prostate cancer, e.g.:

   - Clinically localized disease (≤T2a) and
   - Gleason score 6 (3+3) and
   - Serum PSA <10 ng/mL

   undergoing active surveillance may be enrolled with agreement of the sponsor.
8. A QTc interval of >470 msec by the Fridericia formula (QTcF), at the Screening ECG. If the subject's QTcF is >470 msec on the initial ECG, a total of 3 ECGs should be obtained at least 3 minutes apart and all within 30 minutes. The average of the 3 QTcF's will be used to determine eligibility. Known or suspected causes of prolonged QTc can be treated (e.g., hypocalcemia, hypokalemia, hypomagnesimia) and the ECGs may be repeated. If the subject initiates treatment with a drug known to prolong the QTc during the Screening period after the initial

Screening ECGs were obtained, the Screening ECGs must be repeated once the new drug has reached steady state to ensure the average QTcF remains ≤470 msec. For subject's whose heart rate is <60 bpm, the Bazett correction formula (QTcB) may be used.

9. Subjects who, in the opinion of the Investigator, cannot tolerate intravesical administration or intravesical surgical manipulation (cystoscopy, biopsy) due to the presence of serious comorbid condition(s) (e.g., uncontrolled cardiac or respiratory disorders).
10. Local or severe allergy to any components of the drug regimen.

11.3 Study Withdrawal Criteria

Subjects are free to withdraw from treatment or from any further participation in the study (i.e., withdraw consent) at any time and without prejudice to further treatment. The Investigator should discuss with the subject if they want to withdraw from further treatment only (i.e., additional data will be collected) or from all further study participation at which time no data will be collected for the subject. The investigator must withdraw a subject from all further study participation if that subject withdraws consent. No additional evaluations will be done or data collected for subjects who withdraw consent. All subjects withdrawing from further study treatment should have Post-Treatment evaluation 30 – 37 days after the last dose of study treatment and receive follow up disease evaluation (every 3 months (**Section 10.6**) and until a protocol-defined event as well as be contacted for data secondary endpoint (PFS, OS). The reasons and details relevant to subject withdrawal must be recorded in the case report form (CRF). The Investigator must notify the Medical Monitor if a subject is withdrawn from the study.

Subjects must be withdrawn from study drug for any of the following reasons:

- Withdrawal of informed consent
- Pregnancy (**Section 12.5**)
- Treatment failure (**Section 14.2**)
- Documented extravesical (i.e., upper or lower tract) urothelial carcinoma
- Development of a second malignancy that requires systemic therapy
- Cystectomy
- Unacceptable toxicity
- Persistent non-compliance with the protocol requirements
- Treating physician / study Investigator concludes that it would be in the subject's best interest
- Intercurrent illness that, in the judgment of the Investigator, may affect assessments of clinical status to a significant degree, and that requires discontinuation of study drug.
- Sponsor terminates the study.

Subjects may be considered withdrawn if they fail to return for visits, or become lost to follow-up for any other reason. Every attempt should be made to re-establish contact for subjects who are lost to follow-up (i.e., those subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw). The Investigator should undertake appropriate due diligence and document steps taken to contact the subject (e.g., dates of telephone calls, registered letters).

12 TREATMENT

12.1 Study Drug Administration

Subjects will receive study drug treatments twice weekly (BIW) for 6 weeks and once weekly for 6 weeks during the Induction Phase, and then enter the Maintenance Phase, if eligible (**Table 5**).

Table 5: Treatments

Study Phase	Treatment Regimen
Induction Phase (Weeks 1-12)	One intravesical dose of Vicinium 30 mg in 50 mL of saline instilled twice weekly (BIW) for 6 weeks followed by once weekly for 6 weeks, for a total of 12 weeks. The twice weekly doses are to be administered at least 48 hours apart (and no more than 2 doses may be administered within a calendar week, i.e., within a Sunday through Saturday period.) As an example, while a Monday/Thursday or Tuesday/Friday would be optimal, a Monday/Wednesday or a Tuesday/Thursday dosing schedule could be used. There will be a total of 18 doses over the 12-week period of the Induction Phase.
Maintenance Phase (up to Week 104)	One intravesical dose of Vicinium 30 mg in 50 mL saline instilled once every other week, for up to 24 months (Week 104) from the start of the Induction Phase.

To reduce urine flow during the instillation and dwell of Vicinium in the bladder, subjects will be asked to refrain from drinking any liquids beginning 2 hours prior to study drug instillation through completion of the 2-hour time period during which drug is held in the bladder. Immediately prior to bladder catheter insertion, subjects will empty their bladder. Appropriate study personnel will then insert a catheter into the bladder, and the bladder will be drained.

An appropriate local anesthetic and sterile lubricant may be used at the time of catheterization. In addition, an antibiotic may be given at the discretion of the Investigator. The use of any medications must be recorded on the subject CRF.

Vicinium Administration

Vicinium 30 mg in 50 mL of saline will be instilled through a catheter into the bladder. Subjects will be instructed to hold study drug in the bladder for 2 hours, and asked to refrain from fluid intake to reduce urine flow during this period. After complete administration of the Vicinium dose, the catheter may be clamped and remain in for the 2-hour dwell time, or may be removed, per the discretion of the investigator. Subjects will be required, when physically possible, to be upright (sitting or standing), prone, supine, and in the left and right lateral decubitus positions, for at least 15 minutes each, in any order. If physically unable, this should be recorded in the CRF. At the end of 2-hour period, the catheter will be unclamped and the bladder will be drained (if the catheter remained in place) or the subject will void to empty the bladder.

12.2 Concomitant Medications

In this clinical study, Vicinium will be administered as a monotherapy. Beginning 2 weeks prior to the initial dose of study drug and throughout the time the subject is receiving Vicinium treatment, no other anti-cancer therapies that could affect the disease under study, including radiation therapy, immunotherapy, vaccine therapy, biological therapy, or gene-based therapies will be permitted with the exception that subjects who enter the study with low-risk prostate cancer undergoing active surveillance who, while on study then require androgen-deprivation therapy may be permitted to remain on Vicinium treatment with Sponsor permission. Additionally, no other investigational agent is permitted within 4 weeks before the start of study drug and throughout the time the subject is receiving Vicinium treatment.

Any other medication that is considered necessary for the well-being of the subject, and that is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the Investigator.

All concomitant therapies taken from Screening until the subject has a protocol-defined event must be recorded in the subject's medical record and transcribed to the CRF.

12.3 Treatment Compliance

Study drug administration will take place at the study site under supervision of the Investigator or other authorized clinic staff.

12.4 Randomization and Blinding

This is an open-label, non-randomized study.

12.5 Pregnancy Occurring During the Clinical Trial

It is the responsibility of the Investigator to report to the study Medical Monitor within 24 hours of learning of its occurrence any pregnancy in a subject or in the female partner of a male subject that occurs during the study or within 120 days of the last dose of study drug. If the subject is pregnant, study drug must be discontinued. If the female partner of a male subject is pregnant, the subject may continue on treatment. Barrier contraception must be used or abstinence must be practiced if the male subject continues on treatment. The pregnancy should not be recorded as an adverse event (AE); however, the Investigator will be required to complete a Pregnancy Notification form.

The pregnancy should be followed to determine outcome, including spontaneous or voluntary discontinuation, and the presence of any congenital abnormalities, or maternal and/or newborn complications. Pregnancy follow-up should be recorded on the Pregnancy Follow-up form and reported by the Investigator to the study Medical Monitor. If the pregnancy continues to term, the outcome (health of infant up to a minimum of 6 months of age) must also be reported to the Sponsor or their representative. For any maternal and/or newborn complications, the Investigator should assess if there is a possible relationship to the study drug and evaluate whether it should be reported as an AE or serious adverse event (SAE) (**Section 15.3**). The presence of congenital anomalies must be reported as an SAE.

12.6 Study Drug Interruptions

- In subjects who develop low-grade papillary disease while on treatment, study drug must be interrupted for a minimum of 2 weeks following tumor removal before restarting Vicinium treatment.
- The following criteria will be used for holding Vicinium dosing based on serum creatinine and calculations or measured creatinine clearance:

Baseline Creatinine	Criteria for Holding Vicinium Treatment*	
	Serum Creatinine	Creatinine Clearance
<1.0 mg/dL or <88 µmol/L	>1.5 mg/dL or >133 µmol/L	<40 mL/min or a decrease of 25% from baseline
≥1.0 mg/dL or ≥88 µmol/L	Increase to >1.5x baseline value	<40 mL/min or a decrease of 25% from baseline

*Vicinium dosing should be held if **either** the serum creatinine or the creatinine clearance criteria, as defined in this table, are met.

The investigator should contact the Sponsor for these changes in renal function and the subject should be evaluated for the etiology of these changes. Vicinium treatment may be resumed upon improvement or stabilization at creatinine of ≤2x baseline or ≤2x ULN and with Sponsor agreement.

- Vicinium dosing must be held for any subject whose AST or ALT doubles from their baseline value and is ≥2x ULN; OR for a bilirubin ≥2 mg/dl (≥34 µmol/L). The investigator should contact the Sponsor for these changes in liver function tests and the subject should be evaluated for the etiology of these chances. Vicinium treatment may be resumed upon improvement or stabilization of AST and ALT of ≤2x baseline or ≤2x ULN; OR for a bilirubin ≤2 mg/dl (≤34 µmol/L) and with Sponsor agreement.
- The investigator should consider holding Vicinium treatment for patients with a clinically significant UTI requiring antibiotic therapy until improvement
- Study drug administration must be postponed if a subject develops any Grade 3 or greater adverse event as defined using the NCI-CTCAE version 4.03 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) considered related to Vicinium treatment. Study treatment may resume when the AE returns to ≤ Grade 1 or baseline or sooner **if there is agreement between the investigator and the sponsor**. Study treatment may be postponed at the discretion of the investigator for unrelated AEs, if this is considered in the best interest of the subject. If the causal relationship between Vicinium and an AE is initially uncertain, study drug should be interrupted until that determination is made. Also study treatment may be postponed for lower grade AEs at the investigator discretion if considered in the best interest of the subject.

Missed doses of Vicinium due to interruption of dosing for adverse events should not be made up. In the Maintenance Phase, dosing should be restarted as soon as there is AE resolution i.e., treatment should not be postponed longer in order to align with the initial every-other-week schedule.

If study treatment is postponed longer than 3 weeks, this should be discussed with the Sponsor to determine if the subject should remain on treatment.

The reasons and details relevant to the subject postponement and/or discontinuation of study treatment must be recorded on the CRF. The Investigator must notify the Medical Monitor if study treatment is discontinued.

Subjects discontinuing from study treatment will not be replaced.

13 STUDY DRUG MATERIALS AND MANAGEMENT

13.1 Study Drug

Vicinium™ (oportuzumab monatox) is a clear, colorless solution for intravesical administration. It is provided as a frozen product in a glass vial, and then thawed at room temperature prior to preparation for administration. Cloudiness, a change in color and/or the presence of particulate matter may indicate the product has deteriorated. If this occurs, Eleven Biotherapeutics Inc. should be contacted immediately and the product must not be used.

13.2 Study Drug Packaging and Labeling

Vicinium is packaged in a 10 mL glass borosilicate vial containing 7 mL of study drug at a concentration of 5 mg/mL. Each vial is sealed with a grey butyl stopper and covered with an aluminum cap center tear-off seal.

Vicinium will be mixed with phosphate buffered saline prior to intravesical administration. Refer to the Vicinium Dose Preparation and Administration Manual for details

13.3 Study Drug Accountability

The Investigator agrees that the study drug will be administered only to subjects who have provided written informed consent, have met all entry criteria, and are enrolled in the study. The Investigator must not loan or dispense clinical study material to another Investigator or site.

Drug accountability records will be maintained by the Investigator or authorized site staff for all clinical trial supplies (includes Vicinium and phosphate buffered saline). Eleven Biotherapeutics Inc. or designee will provide the Investigator with drug accountability logs to document receipt and dispensing. Any discrepancy and/or deficiency must be recorded, reported to Eleven Biotherapeutics Inc. or designee, and a plan for resolution documented. If at any point in the conduct of the study a vial is deemed unacceptable for use, the site will document the damage on the drug accountability log and immediately notify Eleven Biotherapeutics Inc. or designee. Eleven Biotherapeutics Inc. or designee will monitor the completeness and accuracy of all accountability records throughout the study and verify product accountability against site documentation. Any expired Vicinium, or Vicinium vial deemed unacceptable for use or any Vicinium supply remaining at the end of the study should be destroyed at each clinical site in accordance with the site's drug destruction policy.

14 ASSESSMENT OF EFFICACY

Standard white-light cystoscopy, urine cytology, and cystoscopic bladder biopsies (directed) will be performed at Screening as described in **Section 10.1**. Fluorescence cystoscopy (e.g., blue light cystoscopy) is acceptable but not required. If a subject undergoes fluorescence cystoscopy for biopsy or TURBT during the screening period, this modality should be used for all on-study biopsies

or TURBTs. However, white-light cystoscopy is appropriate for routine follow-up assessments if a biopsy is not required.

Subjects' disease status will be evaluated based on cystoscopy (and biopsies if indicated) and urine cytology at the end the Induction Phase (week 13) and every 13 weeks during the Maintenance Phase (i.e., Week 26, Week 39, Week 52, Week 65, Week 78, Week 91, Week 104) regardless of dosing interruptions or delays. For subjects who discontinue treatment for reasons other than disease progression (**Section 14.2**), cystectomy or death, the every 13-week disease evaluation should continue for the determination of secondary endpoints e.g., event-free survival, progression-free survival. Every effort should be made to stay on this evaluation schedule, however, a window of one week before and up to 2 weeks after these time points is permitted (e.g., the Week 26 cystoscopy and urine for cytology may be performed from week 25 to week 28, but as close to Week 26 as possible). The complete evaluation to determine disease status may require a repeat cytology and repeat cystoscopy with biopsies (See **Table 7**) and should be completed as soon as possible following the every 13-week timepoint. On cystoscopy, any areas suspicious for disease must be biopsied. In situations where there are no suspicious lesions on cystoscopy but a positive or suspicious result on urine cytology, random bladder biopsies will be obtained from the locations of disease identified at Screening (i.e., by screening biopsies and the screening bladder mapping) and from other areas of the bladder so that all the following areas of the bladder have been biopsied: the dome, the posterior wall, the left and right lateral walls, the trigone and the bladder neck, and in males, the prostatic urethra. A second urine cytology will also be required at the time of evaluation if the result of the first urine cytology is suspicious for urothelial carcinoma. The use of other diagnostic evaluations (e.g. urine FISH) or the performance of additional urine cytology, cystoscopies, and/or biopsies not mandated by the protocol may be performed when clinically indicated per the investigator's clinical judgment or standard of care. Results of urine FISH will not be considered in the response evaluation but may be used by the investigator to guide additional (non-protocol mandated) evaluations.

All cytology and biopsy samples (protocol-mandated or additional per investigator discretion) must be centrally reviewed and graded by an independent pathologist with specific expertise in NMIBC. Instructions for shipping and handling of tissue, cytology and EpCAM samples will be provided in the separate Laboratory Manual for Pharmacokinetics, Anti-Drug/Anti-Toxin Antibodies, Cytology and Tumor Tissue Assessments.

Table 6: Required Tests for Disease Status: Every 13-Week Evaluation

Cystoscopy	1st Urine Cytology	Bladder Biopsies	2nd Urine Cytology
Required	Required	• Directed biopsy of all suspicious-appearing lesions/areas on cystoscopy. • If cystoscopy reveals no suspicious lesions but 1st urine cytology is suspicious or positive for urothelial carcinoma: Biopsy the locations of disease identified at Screening (i.e., by screening biopsies and the screening bladder mapping) and from other areas of the bladder so that all the following areas of the bladder have been biopsied: the dome, the posterior wall, the left and right lateral walls, the trigone and the bladder neck, and in males, the prostatic urethra.	Required if 1st urine cytology is suspicious for urothelial carcinoma

14.1 Criteria for Response (in Subjects with CIS)

The primary endpoint for this study is the complete response rate in subjects enrolled in Cohort 1 (see **Section 10**). These subjects with CIS will be considered to have a complete response if at the time of any disease status evaluation (per protocol every 13 weeks or any unscheduled evaluation) there is no evidence of high-grade disease (CIS, high-grade Ta or high-grade T1 disease) or disease progression (e.g., to muscle invasive disease). Subjects whose initial diagnosis was CIS who are found to have low-grade papillary disease at the time of an evaluation must have the low-grade disease resected by TURBT. Low-grade disease is not considered a treatment failure in these subjects and they may remain on study treatment following TURBT.

14.2 Criteria for Treatment Failure

As defined in this protocol, the term "treatment failure" will refer to events that demonstrate the study drug Vicinium is not able to achieve or maintain a response in the subject's bladder cancer. Specifically, the term "treatment failure" in this protocol is being used to define the following events:

1. Diagnosis at study entry was CIS (with or without papillary disease), high-grade Ta disease or high-grade T1 disease:

   Subjects whose diagnosis at study entry was CIS or high-grade papillary disease will be considered to have a treatment failure if at the time of any disease status evaluation (per protocol every 13 weeks or any unscheduled evaluation) there is evidence of high-grade disease (CIS, high-grade Ta or high-grade T1 disease) or disease progression (e.g., to muscle invasive disease). Subjects who are found to have low-grade papillary disease at the time of evaluation must have the low-grade disease resected by TURBT. Low-grade disease is not considered a treatment failure in these subjects and they may remain on study treatment following TURBT.

2. Initial diagnosis was low-grade T1 disease:

   Subjects whose initial diagnosis was low-grade T1 disease are considered to have a treatment failure if at the time of any disease status evaluation (per protocol every 13 weeks or any unscheduled evaluation) there is evidence of low-grade T1 disease, high-grade disease (CIS, high-grade Ta or high-grade T1 disease) or disease progression (e.g., to muscle invasive disease). Subjects whose initial diagnosis was low-grade T1 disease and who are found to have low-grade Ta disease at the time of evaluation must have the low-grade Ta disease resected by TURBT. Low-grade Ta disease is not considered a treatment failure in these subjects and they may remain on study treatment following TURBT.

3. Subjects with positive urine cytology without histologic, cytologic or radiographic evidence or upper or lower urinary tract malignancy will be considered as no longer in complete response and hence, as having a treatment failure.

14.3 Protocol-Defined Events in the Analysis of Event-Free Survival

Event-free survival (EFS) will be determined for all treated subjects (See **Section 17**). Events in the analysis of EFS include:

- Treatment failure as defined in **Section 14.2**
- Death (as a first event)

Subjects without evidence of a treatment failure who are diagnosed with upper or lower urinary tract urothelial carcinoma by histology, cytology or radiographic evidence as their first event will be censored in the analysis of EFS at the date of diagnosis.

Subjects without evidence of a treatment failure who undergo cystectomy will be censored in the analysis of EFS at the date of cystectomy.

14.4 Criteria for Continuing or Discontinuing Treatment

The results of cystoscopy and biopsies (as indicated), and urine cytology are used to determine disease status and hence, whether subject may remain on treatment (as long as they are tolerating treatment).

The result of these tests will be classified as follows:

Cystoscopy (based on the investigators assessment)

- Negative (No evidence of disease (NED)
- Suspicious (Apparent or suspicious for disease)

Urine Cytology (based on central cytology reading):

- Negative (Negative for high grade urothelial cancer)
- Atypical urothelial cells (This is not considered suspicious for urothelial cancer)
- Suspicious for high-grade disease

- Unsatisfactory
- Low grade neoplasm

Biopsy Findings (based on central pathology reading):

- Positive (for treatment failure, see **Section 14.2**)
- Negative (for treatment failure, see **Section 14.2**).

Table 7: Criteria for Continuing or Discontinuing Vicinium Treatment

Cystoscopy	1st Urine Cytology	Bladder Biopsies[1]	2nd Urine Cytology	Outcome of Assessment
NED	NED	N/R	N/R	Continue Treatment
	Suspicious	Negative	NED	Continue Treatment
			Suspicious	Continue Treatment[2]
			Positive[3]	Off Treatment[2]
	Positive[3]	Negative	N/A	Off Treatment[2]
Suspicious	NED	Negative	N/A	Continue Treatment
	Suspicious	Negative	NED	Continue Treatment
			Suspicious	Continue Treatment[2]
			Positive[3]	Off Treatment[2]
	Positive[3]	Negative	N/A	Off Treatment[2]
Any	Any	Positive[3]	Any	Off Treatment

[1] For purposes of response evaluation, a biopsy is considered positive for treatment failure if, as noted above, the subject's initial diagnosis was high-grade disease and the subject has high-grade disease or disease progression (e.g. to muscle invasive) at response assessment; OR the subject's initial diagnosis was low-grade T1 disease and has any high-grade disease, low-grade T1 disease, or disease progression (e.g. to muscle invasive) at response assessment. Papillary disease that does not meet the criteria for treatment failure should be removed by TURBT and the subject should remain on study treatment.

[2] Any subject with 1 positive or 2 suspicious urine cytology results and negative biopsies for urothelial carcinoma must undergo a workup for upper tract and lower tract disease, e.g., CT/CT urogram or MRI/MRI urogram, ureteral cytology.

[3] A positive biopsy for treatment failure (**Section 14.2**) or a positive urine cytology requires that subjects discontinue treatment

NED: No evidence of disease
N/R: Not required. Does not have to be performed

15 ASSESSMENT OF SAFETY

During the Induction Phase and Maintenance Phase, subjects will be assessed for safety by monitoring of adverse events (AEs), including serious adverse events (SAEs), evaluation of clinical laboratory tests, physical examinations, triplicate ECGs, and vital signs.

15.1 Safety Review Plan

Adverse events including serious adverse events, occurring from the time the subject signs the ICF through 30 days after the last dose of study treatment will be recorded on the appropriate electronic CRF(eCRF). This requirement includes AEs from unscheduled as well as scheduled visits.

Adverse events will be monitored by the study Medical Monitor on an ongoing basis. On a quarterly basis (every 3 months), safety tables and listings will be generated for review.

In addition, an independent data safety and monitoring board (DSMB) will be chartered and operate until all subjects have discontinued treatment. The DSMB charter will conform to applicable regulations and guidance. The DSMB will review aggregated safety data. The DSMB chair will also receive all SAE reports upon generation, regardless of attribution. Details of the DSMB structure and function are included in the DSMB charter.

15.2 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (that may include an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. Any worsening of the subject's pre-existing medical conditions will also be considered an AE, unless it is within the normal range of disease fluctuation for that subject. Pre-existing medical conditions that are stable or improve during the study will be recorded as an AE but will not be considered as treatment-emergent adverse events (TEAEs).

The investigator is responsible for reviewing all laboratory results obtained after a subject signs the ICF through 30 days after the last dose of study drug, whether required by this protocol or for other reasons e.g., evaluation of a pre-existing condition, evaluation and management of an AE. Any abnormal value that leads to a change in the subject's management (e.g., dose interruption, dose reduction, the addition of medication, other medical intervention (e.g., blood transfusion), or increased monitoring) or considered by the investigator to be of clinical significance should be recorded as an AE/SAE.

"Progressive disease" should not be recorded as an AE or SAE. Instead, the diagnoses/syndromes, signs, and/or symptoms associated with a subject's disease progressive should be recorded as AEs, or SAEs if they meet the SAE definition.

All AEs will be assessed using the NCI-CTCAE (version 4.03) (**http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf**).

AEs for which no appropriate CTCAE term exists will be recorded verbatim from the investigator and graded for severity based on CTCAE definitions:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADLs)*.
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death.

A semicolon indicates "or."

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

Assessment of the relationship of the AE to the study drug by the investigator will be based on the following two definitions:

- Not related: A not-related AE is defined as an AE that is not associated with the study drug and can with certainty, be attributed to another cause.
- Related: A related AE is defined as an AE where a causal relationship between the event and the study drug is a reasonable possibility. A reasonable causal relationship is meant to convey that there are facts (evidence such as dechallenge/rechallenge) or other clinical arguments to suggest a causal relationship between the AE and study drug.

If discernible at the time of completing an AE eCRF, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the appropriate AE eCRF. However, if an observed or reported sign, symptom, or clinically significant laboratory anomaly is not considered by the Investigator to be a component of a specific disease or syndrome, then it should be recorded as a separate AE on the appropriate AE eCRF.

15.3 Serious Adverse Events

A serious adverse event (SAE) or serious suspected adverse reaction is considered serious if, in the view of either the Investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE, defined as an AE that, in the view of either the Investigator or the Sponsor, places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death;

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect;
- Inpatient hospitalization or prolongation of existing hospitalization. The following will not be considered as a hospitalization for the criteria of an SAE:
    - Elective or pre-planned hospital stays for conditions that existed prior to informed consent and have not worsened after the subject signed the ICF. However, if any surgical or procedural complication results in prolongation of a pre-planned hospitalization, this must be reported as an SAE.
    - Hospital stays or prolongation of a hospital stay for social reasons.
    - Events that result in a hospital stay or emergency room visit for less than 24 hours if this is the only SAE criterion being met.
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs, regardless of suspected causality, occurring from the time a subject signs the Informed Consent and until 30 days after study drug discontinuation must be reported to the sponsor within 24 hours of learning of its occurrence.

The minimum information required for SAE reporting includes the identity of the investigator, site number, subject number, event description, SAE term(s), reason why the event is considered to be serious (i.e., the seriousness criteria), and investigator's assessment of the relationship of the event to study drug. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study drug because of the event, and the outcome/resolution of the event should be recorded on the eCRF.

When reporting SAEs, the following guidance should be followed:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than the signs or symptoms of the diagnosis/syndrome. Signs and symptoms may then be described in the event description.
- "Death" should not be reported as an SAE term, but as an outcome of a specific SAE, unless the event preceding the death is unknown. In the case where the events leading to death are unknown, "death" may be used as an event term. If an autopsy is performed, the report should be provided.

- "Progressive Disease" should not be reported as an SAE. Instead, diagnoses/syndromes, signs, and/or symptoms associated with a subject's disease progressive should be recorded as AEs or SAEs if they meet the SAE definition.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by Eleven Biotherapeutics or its designee.

The Investigator is responsible for promptly notifying the institutional review board (IRB) of all SAEs, including follow-up information, and a copy of that report must be retained at the study site for review by the Sponsor or designee upon request.

15.4 Expedited Safety Reporting

Eleven Biotherapeutics or its designee will evaluate all SAEs as soon as the report is received. SAEs that are unexpected and for which there is a reasonable possibility that the drug caused the AE will be reported to regulatory authorities in an expedited manner. An AE is considered "unexpected" if it is not listed in the most recent version of the investigator brochure or is not listed at the specificity or severity that has been observed.

The investigator at each clinical site is responsible for reporting SAEs in accordance to his or her IRB/EC's SOPs and policies. The investigator is responsible for maintaining documentation demonstrating that the IRB/EC was properly notified.

Eleven Biotherapeutics Inc. or its representative will provide details to the Investigator of all serious, unexpected and related AEs (or other events depending on the specific requirements) that should be reported to IRBs as appropriate.

15.5 Follow Up of Adverse Events

Any clinically significant AE (e.g. an AE leading to study drug discontinuation) or any SAE assessed as related to study drug that is ongoing at the time of the Post-Treatment assessment (i.e., 30-37 days after the last dose of study drug) must be followed until either resolution of the event or determination by the investigator that the event has become stable or irreversible. This follow-up guidance also applies to related SAEs that occur >30 days after the last dose of study drug.

16 STUDY ASSESSMENTS

Study assessments will be obtained for each subject according to the study schedule in **Sections 10.1 – 10.5**, **Table 3** and **Table 4**.

16.1 Demographics and Medical / Cancer History

Demographic assessment at screening will include date of birth, sex, ethnicity, and race. Cancer history will include all cancer diagnoses and treatment, including surgery, local therapies, systemic therapies (e.g., chemotherapy, targeted therapy, biologic agents [immunologic agents, antibodies]), and radiation therapy, including investigational agents and treatments. Medical history will include all other medical and surgical history, cigarette use, alcohol and illegal drug use, and concomitant medications.

16.2 Laboratory Assessments

All clinical laboratory results will be reviewed by the Investigator. Laboratory test are as follows:

- Serum chemistry, including total bilirubin, ALT, AST, alkaline phosphatase, albumin, lactate dehydrogenase, BUN, creatinine, glucose, sodium, potassium, bicarbonate, chloride, calcium, magnesium, phosphorus, lipase, amylase
- Urinalysis including glucose, protein. red blood cells (RBC) and white blood cells (WBC) by dipstick and microscopic evaluation for RBCs and WBC counts
- Hematology, including Complete Blood Count (CBC) with differential, hemoglobin, hematocrit, and platelets.
- Pregnancy tests (serum or urine) for women of childbearing potential

16.3 Physical Examination

During the Baseline Period, a complete physical examination including head, eyes, ears, nose, and throat (HEENT), height, weight, skin, lymphatic, respiratory, cardiovascular, gastrointestinal, genitourinary, neurologic, and musculoskeletal systems should be completed. Subjects' height and weight should be measured at baseline. Weight will be recorded every 4 weeks. While the subject is on treatment and at the post-treatment visit, the physical examination should be targeted for evaluation of AEs, i.e., a history or symptom-directed physical examination.

16.4 Electrocardiogram (ECG)

A single 12-lead ECG will be performed at Screening to determine subject eligibility. If the subject's QTcF is >470 msec on the initial Screening ECG, a total of 3 ECGs should be obtained at least 3 minutes apart and all within 30 minutes. The average of the 3 QTcF's will be used to determine eligibility. Known or suspected causes of prolonged QTc can be treated (e.g., hypocalcemia, hypokalemia, hypomagnesemia) and the ECGs may be repeated. If the subject initiates treatment with a drug known to prolong the QTc during the Screening period after the initial Screening ECGs were obtained, the Screening ECGs must be repeated once the new drug has reached steady state to ensure the average QTcF remains ≤470 msec. For subject's whose heart rate is <60 bpm, the Bazett correction formula (QTcB) may be used.

Triplicate ECGs (consisting of three individual ECGs obtained within 30 minutes of each other at least 3 minutes apart) will be obtained on treatment and at the Post-Treatment evaluation. The ECGs should be initiated after at least 10 minutes of quiet rest in a supine position.

16.5 Vital Signs

Vital signs: blood pressure, pulse, respirations and temperature.

16.6 Pharmacokinetics Assessments

Plasma samples will be collected for Vicinium PK evaluation on

- Week 1 Day 1: pre-dose and after the 2 hour dwell time i.e., within 30 minutes of the bladder being drained or the subject voids the drug
- Week 6 Second Dose: After the 2 hour dwell time i.e., within 30 minutes of the bladder being drained or the subject voids the drug

- Week 12: After the 2 hour dwell time i.e., within 30 minutes of the bladder being drained or the subject voids the drug

Note: For subjects who develop renal or hepatic AE considered possibly related to Vicinium treatment or for any SAE, an additional PK sample may be requested by the Sponsor to help in the evaluation of the AE.

Refer to the Laboratory Manual for Pharmacokinetic, Anti-Drug/Anti-Toxin Antibodies, Cytology and Tumor Tissue Assessments for this study for additional details.

16.7 Biomarker Assessment

- Anti-Vicinium antibodies
  Note: For subjects who develop renal or hepatic AE considered possibly related to Vicinium treatment or for any SAE, an additional anti-Vicinium antibody sample may be requested by the Sponsor to help in the evaluation of the AE.
- EpCAM expression by IHC on all tumor biopsies positive for NMIBC. Five unstained tissue slides are requested when these are available. Refer to the Laboratory Manual for Pharmacokinetic, Anti-Drug/Anti-Toxin Antibodies, Cytology and Tumor Tissue Assessments for this study for additional details.
- Other biomarkers that may be associated with response or disease progression or treatment failure and that may include, for example, tumor subtype morphology, furin levels in tumor cell endosomes, presence of a glycosaminoglycan coat, and presence of receptors that could impede a host anti-tumor immune response such as PD-L1, may be evaluated on all tumor biopsies positive for NMIBC, if additional tumor unstained slides are available. Preference will be given to EpCAM expression (as described above). An additional 5 – 10 slides, when available, should be submitted. Refer to the Laboratory Manual for Pharmacokinetic, Anti-Drug/Anti-Toxin Antibodies, Cytology and Tumor Tissue Assessments for this study for additional details**. NOTE**: For subjects who have enrolled in the study on protocol versions prior to Version 4.0, additional slides will not be requested from prior biopsies positive for NMIBC.

17 STATISTICS

17.1 General Principles of Statistical Analysis

The type I (alpha error) for all hypothesis testing will be set at 0.05, and all statistical tests will be two-sided. All confidence intervals will be two-sided 95% confidence intervals. Data will be summarized by reporting the frequency and percentage of subjects in each category for categorical and ordinal measures, and means, standard deviations (SD), medians, minimum and maximum for continuous measures.

17.2 Analysis Populations

Modified Intent-to-treat (mITT) Population: The mITT population includes any subject who receives at least one dose of study medication and has an evaluable baseline assessment of disease (biopsy, cystoscopy, and cytology). The mITT population will be a supplementary efficacy analysis population.

Primary Efficacy Population: The primary efficacy population includes any subject in the mITT population who has "early refractory/relapsed" CIS or CIS plus papillary disease (see **Section 17.5**). This will be the primary population utilized for the evaluation of efficacy.

Safety Population: The safety population includes any subject who receives at least one dose of study medication.

17.3 Subject Disposition, Demographics and Other Baseline Characteristics

The number of subjects enrolled into the study, the number in each analysis population, major protocol violations, number of subjects who discontinue early, reasons for discontinuation, and duration of treatment will be summarized in tabular format.

Demographic and background characteristics (including baseline medical history) will be summarized descriptively.

17.4 Study Drug Exposure and Concomitant Medication

Exposure to study drug will be summarized with quantitative descriptive statistics.

Concomitant therapy (i.e., any medication other than the investigational study product taken by the subject during the study) will be summarized and coded according to World Health Organization preferred term using the safety population. Subject incidence will be tabulated by preferred term.

17.5 Analysis of Efficacy

The primary efficacy analysis will be based on the complete response (CR) rate and duration of response in subjects in Cohort 1 (see **Section 10**). The number and percentage of subjects with CIS with or without papillary disease with a complete response will be summarized separately at each response assessment. Ninety-five percent (95%) confidence intervals around the complete response rate will be calculated using the Clopper-Pearson method. For subjects with CIS with or without papillary disease who achieve complete response, the duration of response, defined as the start of the complete response to the first documented case of treatment failure (see **Section 14.2)** or death, will be estimated using the method of Kaplan-Meier. Any subject who does not experience treatment failure or death will be censored at the last non-missing assessment.

All subjects will be included in the analysis of event-free survival (EFS). EFS will be estimated using the method of Kaplan-Meier. Protocol-defined events in the analysis of event-free survival are:

- Treatment failure (see **Section 14.2**). Subjects with a treatment failure that their post-Induction Phase assessment will be considered to have a treatment failure on study Day 1.
- Death (as a first event)

Subjects without evidence of a treatment failure who are diagnosed with upper or lower urinary tract urothelial carcinoma by histology, cytology or radiographic evidence as their first event will be censored in the analysis of EFS at the date of diagnosis.

Subjects without evidence of a treatment failure who undergo cystectomy will be censored in the analysis of EFS at the date of cystectomy.

Subjects who do not experience an event will be censored at the last non-missing assessment. Subjects with persistent disease during the Induction Phase (i.e., disease at the Post-Induction Phase evaluation) will be treated as having an event at Day 1. The ninety-five percent (95%) confidence

interval around the event-free survival rate at 18 months will be presented. Analyses of other time-to-event efficacy endpoints (time to cystectomy, time to disease recurrence, time to progression, progression-free survival, and overall survival) will be analyzed in a similar manner.

- Time to cystectomy: defined as the time from the date of first dose of study treatment to surgical bladder removal
- Time to disease recurrence: defined at the time from the date of first dose of study treatment to treatment failure or disease progression (e.g., T2 or more advanced disease)
- Time to progression (TTP): defined at the time from the date of first dose of study treatment to disease progression (e.g., T2 or more advanced disease) or death as a first event
- Overall survival (OS): defined at the time from the date of first dose of study treatment to death from any cause

Subset analyses using the mITT population by pathology at study entry will be performed as determined by final distribution.

17.6 Analysis of Safety

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). The NCI-CTCAE 4.03 terms are grouped by MedDRA Primary SOCs. Separate tables and/or listings for will be provided for AEs by maximum intensity, treatment-emergent AEs, relationship to study medication, discontinuation of study medication, and death. Tabulations and listings of values for vital signs and clinical laboratory tests will be presented. The tabulation of clinical laboratory tests will be classified as falling above, below, or within normal range. Follow-up ECG and physical examination data will be summarized in tabular format.

17.7 Interim Analysis

No formal interim analysis is planned.

17.8 Sample Size and Power

Assuming the true complete response rate at 12 months is 30%, sample sizes associated with various widths of a two-sided, exact (Clopper-Pearson) 95% confidence intervals are provided in the table below:

Sample Size (N)	Target Distance from P to Lower Limit	Proportion (P)	Lower Limit
121	0.080	0.300	0.220
95	0.090	0.300	0.210
76	0.100	0.300	0.200

Under the provided assumptions, a sample size of ≥77 evaluable subjects in Cohort 1 (see **Section 10**) is sufficient to estimate complete response rate with an exact 95% confidence interval that excludes 0.2 (PASS 2008).

The secondary endpoint of event-free survival (EFS) will be used to assess the treatment effect in all subjects, i.e., those with CIS (with or without papillary disease) and those with papillary-only

disease. An estimate of EFS at the 18 month time-point will be calculated. The total sample size of 134 subjects will provide at least 80% power to test the null hypothesis that the event-free survival rate at 18 months is 20% versus the alternative hypothesis that the event-free survival rate at 18 months is ≥30%. This calculation is based on the assumptions of a nonparametric distribution for event-free survival and the length of follow-up is 24 months.

18 DATA COLLECTION, STUDY MONITORING, DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

To assure the accuracy and completeness of data collected in the electronic case report forms (eCRFs), it is mandatory that representatives of Eleven Biotherapeutics Inc., or its representatives, as well as representatives of regulatory authorities (e.g., FDA or Health Canada), have access to original source documents (e.g., subject records, subject charts, and laboratory reports).

Eleven Biotherapeutics Inc. reserves the right to terminate the study at any site where the Investigator refuses to supply source documentation of work performed in the clinical study.

18.1 Subject Numbering

At Screening, subjects who provide informed consent for the study will be assigned a consecutive screening number beginning with 0001. If a subject is re-screened, a new screening number will be assigned. Upon confirmation of a subject's continued eligibility, a 4-digit treatment number is then assigned. A treatment number should not be assigned until the Investigator receives documented confirmation of disease by the protocol-specified, independent central pathology reviewer.

18.2 Data Collection

An electronic data capture system (EDC) will be utilized in this study to collect subject data. All users of the EDC system must first be trained before being able to access the system.

All eCRFs should be filled out completely for each enrolled subject. For subjects who fail to qualify for study enrollment (i.e. Screen Failures), the screening visit date, Informed Consent date, demographics, Inclusion/Exclusion information, central pathology results (if applicable) and eligibility data will be entered into the system. No other eCRFs will be completed. The Investigator will review and sign off on the eCRF casebook upon completion of data collection for each subject.

The completed eCRFs are the sole property of Eleven Biotherapeutics Inc.

18.3 Study Monitoring

Before study initiation, at a site initiation visit or at an Investigator's meeting, a Eleven Biotherapeutics Inc. representative, or designee, will review the protocol and eCRFs with the Investigators and their study site staff. During the study, a monitor will visit the site regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The Investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, contact notes, laboratory data, and the results of any other tests or assessments. All information on

eCRFs must be traceable to these source documents in the subject's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data. The Investigator must also keep the original Informed Consent form signed by the subject (a signed copy is given to the subject).

18.4 Audits and Inspections

Eleven Biotherapeutics Inc. Quality Assurance or their representatives may conduct audits at the study site(s). Audits will include, but are not be limited to: compliance with the protocol, compliance with IRB procedures, audit trail of data handling and processes, Standard Operating Procedures, drug supply, presence of required documents, informed consent process, and comparison of data on eCRFs with source documents. The Investigator agrees to accommodate and participate in audits conducted at a reasonable time and manner, as needed.

Regulatory authorities may also audit the Investigator during or after the study. The Investigator should contact Eleven Biotherapeutics Inc. immediately if this occurs. Additionally, the Investigator must fully cooperate with governmental (e.g., FDA or Health Canada) audits.

19 QUALITY CONTROL AND QUALITY ASSURANCE

All clinical work conducted under this protocol is subject to GCP and ICH guidelines. The study will be subject to inspection by regulatory authorities (e.g., FDA or Health Canada) and Eleven Biotherapeutics Inc. or its representatives, and will be monitored by authorized personnel to ensure adherence to the protocol and these regulations and guidelines. The purpose of these efforts is to ensure that the trial is conducted and data are collected, documented, and reported in compliance with the protocol, GCP, and all applicable regulatory requirements.

The Investigator agrees to give access to all relevant data and records to Eleven Biotherapeutics Inc., clinical Quality Assurance representatives, monitors, and auditors, as well as to Institutional Review Boards/Independent Ethics Committees (IRBs/IECs) and regulatory authorities, as required. If an inspection of the clinical site is requested by a regulatory authority, the Investigator must inform Eleven Biotherapeutics Inc. immediately that this request has been made. It is the responsibility of the Investigator and their relevant personnel to be available during the monitoring visits and possible audits and that sufficient time is devoted to the process.

By signing the Informed Consent form, a study subject authorizes access to his/her confidential medical records by the Sponsor’s clinical monitor and/or regulatory authorities for the purpose of comparing these source documents with subject eCRFs, and to verify compliance with the protocol.

20 ETHICS

This clinical study is designed and shall be implemented and reported in conformance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, and in accordance with FDA regulations and guidelines and applicable federal, state, and local laws, and with the ethical principles laid down in the Declaration of Helsinki. Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study accordingly.

20.1 Independent Ethics Review

It is the responsibility of the Investigator to obtain approval of the protocol, Informed Consent form, and any other documents or information that are likely to be presented to the subject by a properly constituted IRB/IEC. Copies of IRB/IEC approvals must be forwarded to Eleven Biotherapeutics Inc. before study initiation. The IRB/IEC must agree to review the study progress periodically, at intervals not to exceed 1 year and give yearly written approval to continue the study. A copy of this approval, referring to study title and number, must be forwarded to Eleven Biotherapeutics Inc.

The Investigator must also provide any revisions to the Informed Consent form or protocol amendments to the IRB/IEC for approval, and forward copies of the approval to Eleven Biotherapeutics Inc. Any revisions that may increase subject risk exposure must be approved by the IRB/IEC prior to implementation. Administrative changes (such as changes in address and phone number) must be sent to IRBs/IECs, but do not require approval.

In addition, the Investigator is responsible for reporting any serious or unexpected AEs to the IRB/IEC.

20.2 Subject Information and Informed Consent

It is the responsibility of the Investigator to provide each subject (or the subject's legally authorized representative) full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved before inclusion in the trial.

Eligible subjects may only be included in the study after providing signed, written (witnessed, where required by law or regulation), IRB- or IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. A copy of the Informed Consent form must be given to each subject. Subjects must be informed of their right to withdraw from the trial at any time.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol, including Screening procedures). The process of obtaining informed consent should be documented in the subject source documents.

21 RETENTION OF RECORDS

The Investigator agrees to keep study-related records, including identity of all study participants, original signed and dated Informed Consent forms, copies of all CRFs, source documents, and detailed records of drug disposition and all other study-specific documentation in accordance with ICH Guidelines to enable evaluations or audits from regulatory authorities or Eleven Biotherapeutics Inc. or its representatives. ICH requires the following:

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

22 PUBLICATION POLICY

All information obtained during the conduct of this study will be regarded as confidential, and written consent from the Sponsor is required prior to disclosing any information relative to this study. Copies of any publication, written presentation of data, or script of an oral presentation of the data must be provided to the Sponsor at least 30 days prior to submission for publication or presentation. This requirement is to assure concurrence regarding data, evaluations, and conclusions, as well as to communicate any new or unpublished information that may be relevant, and to protect the Sponsor's intellectual property.

Nothing in this agreement is intended to imply that either the Sponsor or the Investigator(s) can prevent publication of the results.

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APPENDIX 1: KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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