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Official Title: A Phase 3, Single-arm, Multicenter Study to Evaluate the Efficacy and Safety of UGN-103, a Novel Formulation of UGN-102, for the Treatment of Patients With Low-grade (LG) Non-muscle Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence (UTOPIA)

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Protocol Number: BL013

Compound: UGN-103 (mitomycin) for intravesical solution

Study Phase: 3

Short Title: A Phase 3 Single-arm Study of UGN-103 for the Treatment of LG IR NMIBC

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STATEMENT OF COMPLIANCE

The study will be conducted according to the protocol and in compliance with International Council for Harmonisation Good Clinical Practice (ICH GCP), the applicable United States (US) Code of Federal Regulations (CFR), and European Union Clinical Trials Regulation 536/2014 (EU CTR). The principal investigator (PI) will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor, except where necessary to eliminate an immediate hazard(s) to the study patients.

The protocol, informed consent form(s) (ICF), recruitment materials, and all patient materials will be submitted to the institutional review board (IRB)/independent ethics committee (IEC) for review and approval according to country-specific requirements. Approval of both the protocol and the ICF must be obtained before any patient is enrolled. Any amendment to the protocol will require review and approval by the IRB/IEC before the changes are implemented to the study. All changes to the ICF will be IRB/IEC approved; a determination will be made regarding whether a new consent needs to be obtained from patients who provided consent using a previously approved ICF.

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Single-arm, Multicenter Study to Evaluate the Efficacy and Safety of UGN-103, a Novel Formulation of UGN-102, for the Treatment of Patients With Low Grade (LG) Nonmuscle Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence (UTOPIA)

Short Title: A Phase 3 Single-arm Study of UGN-103 for the Treatment of LG IR NMIBC

Rationale: UroGen is developing UGN-103, a reformulation of the mitomycin lyophilized powder in UGN-102, to simplify the reconstitution procedure and considerably shorten the manufacturing process. [redacted] UroGen proposes to conduct a clinical endpoint study in adult patients with LG IR NMIBC using the new formulation (UGN-103) [redacted]. The data from this study will be descriptively compared with the results from Phase 3 Study BL011 and Phase 2 Study BL005 using the original formulation (UGN-102).

Objectives and Endpoints

Objective	Endpoint
Primary	
• To evaluate the tumor ablative effect of UGN-103, a novel formulation of UGN-102, in patients with LG NMIBC	• CRR, defined as the proportion of patients who achieved CR at the 3-month Visit (3 months after the first instillation of UGN-103) as determined by cystoscopy, for cause biopsy, and urine cytology
Secondary	
• To evaluate the durability of response with respect to DOR and DCR rate at scheduled disease assessment time points	• DOR in patients who achieved CR at the 3-month Visit, defined as the time from the date of evidence of CR at the 3-month Visit to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, or death due to any cause, whichever occurred first • DCR rate at scheduled disease assessment time points, defined as the proportion of patients who achieved CR at the 3-month Visit and maintained CR (ie, no detectable disease) up to that particular follow-up disease assessment
• To evaluate the safety and tolerability of UGN-103 in patients with LG NMIBC	• Safety and tolerability will be evaluated through the reporting of AEs, including SAEs and AESIs, and through standard clinical and laboratory tests (eg, hematology and chemistry, urinalysis, physical examination, and vital signs)
• To assess the PK profile of mitomycin in plasma in a subgroup of patients treated with UGN-103	• Concentration data and PK parameters (C_{max}, t_{max}, and AUC)
Exploratory	
• To assess the effect of UGN-103 on PRO measures including disease related quality of life and treatment satisfaction	• Changes from baseline in patient scores on the QLQ-C30 and TSQM questionnaires
• To identify mechanisms of sensitivity and/or resistance to UGN-103	• DNA, RNA and/or protein biomarkers in tumor tissue
• To evaluate preliminary responses following SoC treatment in patients who have an NCR at the 3-month Visit	• Number (%) of response outcomes evaluated at the first disease assessment visit after SoC

AE = adverse event; AESI = adverse event of special interest; AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; CR = complete response; CRR = complete response rate; DCR = durable complete response; DNA = deoxyribonucleic acid; DOR = duration of response; LG = low grade; NCR = non-complete response; NMIBC = non-muscle invasive bladder cancer; PK = pharmacokinetic(s); PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire for Cancer Patients; RNA = ribonucleic acid; SAE = serious adverse event; SoC = standard of care; t_{max} = time to maximum plasma concentration; TSQM = Treatment Satisfaction Questionnaire for Medication.

Overall Design

This Phase 3, single-arm, multicenter study will evaluate the efficacy and safety of UGN-103, a novel formulation of UGN-102, instilled in the urinary bladder of patients with LG NMIBC.

Patients who provide informed consent will undergo a Screening Visit to determine eligibility. The Screening Period is up to 35 days for all patients. Screening procedures are to provide evidence of LG NMIBC and no evidence of high grade (HG) disease, and every effort should be made to minimize the time interval between diagnosis and treatment.

Eligible patients will be treated with UGN-103 once weekly for 6 weeks (a total of 6 doses).

Efficacy will be assessed by the complete response rate (CRR) at the 3-month Visit (approximately 3 months after the first instillation). Response will be determined based on visual observation (white light cystoscopy), histopathology of any remaining or new lesions by central pathology lab (if applicable), and interpretation of urine cytology by central pathology lab. Any lesions or suspect tissue must be biopsied to evaluate for persistence of disease.

Patients who have a complete response (CR) at the 3-month Visit, defined as having no detectable disease (NDD) in the bladder, will enter the Follow-up Period of the study. During the Follow-up Period, patients will return to the clinic every 3 months for evaluation of response. Patients will remain on study until disease recurrence, disease progression, death, or the last patient completes 12 months of follow-up (ie, 12 months after the 3-month Visit), whichever occurs first.

Patients who have a non-complete response (NCR) at the 3-month Visit will undergo investigator designated standard of care (SoC) and have a separate End of Study (EOS) Visit performed.

Safety will be evaluated based on review of adverse events (AEs) and changes in laboratory assessments, physical examinations, and vital signs. All safety data will be reviewed on an ongoing basis by the sponsor, including close review and follow up of any unexpected AE assessed as related to UGN-103 and qualified per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 as Grade 3 or 4.

Inclusion Criteria

1. Provide written informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2. Patient must be $\geq$ 18 years of age at the time of informed consent.

3. Patient who has LG NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening. Note: This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of the tumor is not to be performed. Residual tumor must be present and documented after biopsy and before instillation of study treatment.

4. History of at least 1 prior episode of NMIBC. Note: This refers to a previous episode(s) and not to the current episode for which the patient is being screened.

5. Has intermediate risk disease, defined as having 1 or 2 of the following:

   a. Presence of multiple tumors.

   b. Solitary tumor > 3 cm.

   c. Early or frequent recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis at the initial Screening Visit).

   Note: Patients with all 3 factors are considered high risk and are not eligible to participate.

6. Negative voiding cytology for HG disease within 8 weeks before Screening.

7. Has adequate organ and bone marrow function as determined by routine laboratory tests as below:

   - Leukocytes ≥ 3,000/μL (≥ 3×10^9/L).
   - Absolute neutrophil count ≥ 1,500/μL (≥ 1.5×10^9/L).
   - Platelets ≥ 100,000/μL (≥ 100×10^9/L).
   - Hemoglobin ≥ 9.0 g/dL.
   - Total bilirubin ≤ 1.5 × upper limit of normal (ULN).
   - Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) ≤ 2.5 × ULN.
   - Alkaline phosphatase (ALP) ≤ 2.5 × ULN.
   - Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min.

8. Has an anticipated life expectancy of at least the duration of the trial.

9. Both male and female patients:

   Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   a. Female partner of male patient:

   Willing to use 2 acceptable forms of effective contraception from enrollment through 6 months post treatment if the female partner is of childbearing potential (defined as premenopausal women who have not been sterilized).

   Acceptable methods of birth control which are considered to have a low failure rate (ie, less than 1% per year) when used consistently and correctly, such as implants, injectable, combined (estrogen/progesterone) oral contraceptives, intrauterine devices (only hormonal), condoms with spermicide, sexual abstinence* or vasectomized partner.

* Sexual abstinence is defined as refraining from intercourse from enrollment through 6 months post treatment. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is NOT an acceptable method of contraception.

b. Female patient:

Willing to use 2 acceptable forms of effective contraception from enrollment through 6 months post treatment if the patient is of childbearing potential (defined as premenopausal women who have not been sterilized).

Exclusion Criteria

1. Received Bacillus Calmette-Guérin (BCG) treatment for urothelial carcinoma (UC) within the previous 1 year.
2. History of HG bladder cancer (papillary or carcinoma in situ [CIS]) in the past 2 years.
3. Known allergy or sensitivity to any component of the study treatment (including excipients) that in the investigator's opinion cannot be readily managed.
4. Clinically significant urethral stricture that would preclude passage of a urethral catheter.
5. History of:
   a. Neurogenic bladder.
   b. Active urinary retention.
   c. Any other condition that would prohibit normal voiding.
6. Past or current muscle invasive bladder cancer (ie, T2, T3, T4) or metastatic UC.
7. Current tumor stage of T1.
8. Concurrent upper tract urothelial carcinoma (UTUC).
9. Evidence of active urinary tract infection (UTI) that in the investigator's opinion cannot be treated and resolved prior to biopsy and/or administration of study treatment.
10. Is pregnant or breastfeeding.
11. Has an underlying substance abuse or psychiatric disorder such that, in the opinion of the investigator, the patient would be unable to comply with the protocol.
12. History of prior treatment with an intravesical chemotherapeutic agent in the past 2 years except for a single dose of chemotherapy immediately after any previous transurethral resection of bladder tumors (TURBT).

13. Has participated in a study with an investigational agent or device within 30 days of enrollment.

14. Has previously participated in a study in which they received UGN-102.

15. Has any other active malignancy requiring treatment with systemic anticancer therapy (eg, chemotherapy, immunotherapy, radiation therapy). Superficial cancers such as cutaneous basal cell or squamous cell carcinomas that can be treated locally are allowed.

16. Has any other clinically significant medical or surgical condition that in the investigator's opinion could compromise patient safety or the interpretation of study results.

17. Where applicable per country regulation, the patient must not be currently committed to an institution by virtue of an order issued by either judicial or administrative authorities.

Intervention Groups and Duration: Patients will receive UGN-103 once weekly for 6 weeks (a total of 6 doses). The dose of UGN-103 to be instilled is [redacted] mg mitomycin per [redacted] mL sterile hydrogel via urethral catheter, with a total instillation volume of [redacted] mL ([redacted] mg mitomycin).

The approximate total duration of study participation for each patient (first instillation to last visit) will range from 15 to 21 months assuming a 6-month enrollment period.

Statistical Considerations

Statistical Hypothesis: No formal hypothesis will be tested for the confirmation of efficacy. A hypothesis is provided only for the justification of sample size.

Sample Size: Approximately 87 patients will be enrolled.

Statistical Analyses: The sample size calculation is based on the level of precision of the estimated CRR. For an observed CRR of 60.9%, the 95% exact confidence interval (CI) is (49.8%, 71.2%) with 87 patients. Assuming a CRR of 60% in the study as compared to 45%, using a binomial exact test, the power is 79.2% with 87 patients to demonstrate statistical significance at a 1-sided alpha of 0.025.

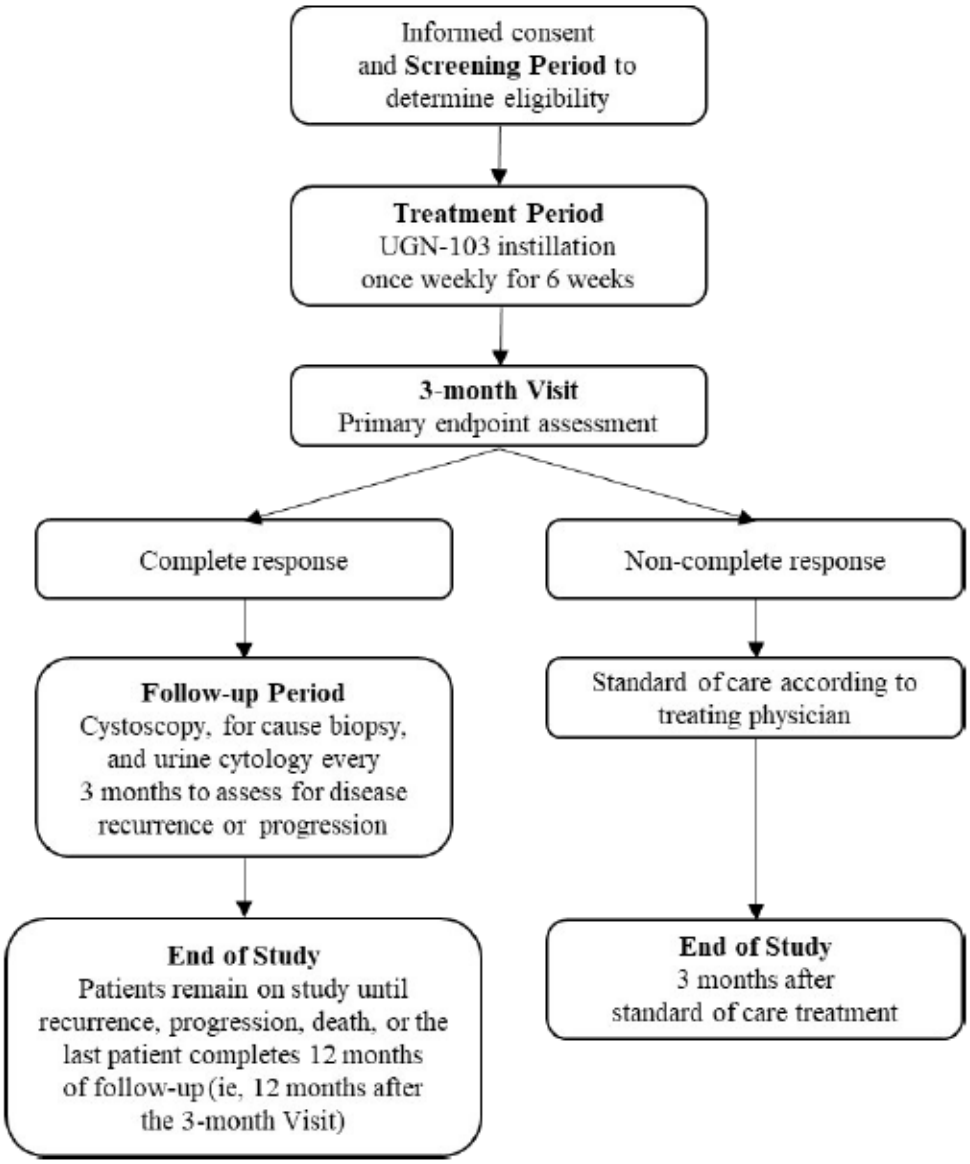
Point estimates and 95% exact CIs of the primary endpoint CRR at the 3-month Visit and secondary endpoint durable complete response (DCR) rate at scheduled disease assessment time points will be summarized. Duration of response (DOR) will be estimated using the Kaplan-Meier method. Safety data will be analyzed descriptively. The safety analysis set that includes all patients who received any dose of UGN-103 will serve as the primary population for the analyses of efficacy and safety data in this study.

The pharmacokinetic (PK) analysis set includes patients in the safety analysis set who provide consent for PK samples and have at least 1 plasma sample for evaluation of PK properties of mitomycin. The plasma concentration versus time profiles collected for mitomycin will be

summarized using descriptive statistics for pre-dose and 0.5, 1, 2, 3, 4, 5, and 6 hours after the first instillation of UGN-103 for patients in the PK analysis set.

No formal interim analysis is planned for this study. The final analysis will be performed after all patients have completed the study, withdrawn consent, been lost to follow-up, died during the study, or when the study is closed by the sponsor.

1.2 Schema



1.3 Schedule of Activities

Procedures	Screening Period [a]	Treatment Period							3-M DAV [b]	Follow-up Period [c] (On-site visit every 3 months after the 3-M DAV)					EOS (NCR only)
Day/Week/Month	D-35 to D-1	D1/ W1	D8/ W2	D15/ W3	D22/ W4	D29/ W5	D36/ W6	TC 1 M2	M3	TC 2 M4	TC 3 M5	M6	TC 4 M7	M9 to EOS [d]	SoC + 3 m
Window [e]	NA	D-1 + 7 d	-1/ + 3 d	-1/ + 3 d	-1/ + 3 d	-1/ + 3 d	-1/ + 3 d	± 1 w	± 1 w	± 1 w	± 1 w	+ 2 w	± 1 w	+ 2 w	± 1 w
Informed consent	X [f]														
Inclusion/exclusion criteria	X														
Demographics	X														
Medical/surgical and smoking history	X														
Concomitant medication review	X [g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
General physical examination [h]	X														
Urological examination [i]	X	X	X	X	X	X	X								
Height and weight	X														
Vital signs [j]	X	X	X	X	X	X	X		X			X		X	
Hematology/serum chemistry (central lab)	X	X	X	X	X	X	X		X			X			
Urinalysis [k]	X	X	X	X	X	X	X		X			X		X	
Pregnancy test (WOCBP only) [l]	X	X						X	X	X	X	X	X		
AE review and evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT urogram, retrograde pyelogram, or MRI [m]	X														
Cystoscopy (white light) [n]	X								X			X		X	
Cold cup biopsy (send to central lab) [n]	X														
Urine cytology (send to central lab)	X [o]								X			X		X	
Administer QLQ-C30 [p]	X						X		X			X		X	
Administer TSQM [p]							X		X			X		X	
Archival biopsy [q]	X														
Biopsy remaining lesions if indicated by cystoscopy (send to central lab)									X			X		X	
Administer study treatment		X	X	X	X	X	X								
PK (in a subgroup of 9-12 patients) (send to central PK lab)		X [r]													
Complete eCRFs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess outcome of SoC treatment [s]															X

AE = adverse event; CR = complete response; CT = computed tomography; d = day(s); D = visit day; DAV = disease assessment visit; eCRF = electronic case report form; EOS = end of study; HG = high grade; LG = low grade; m = month(s); M = visit month; min = minute(s); MRI = magnetic resonance imaging; NA = not applicable; NCR = non-complete response; NMIBC = non-muscle invasive bladder cancer; PK = pharmacokinetic(s); QLQ-C30 = Quality of Life Questionnaire for Cancer Patients; SoC = standard of care; TC = telephone contact; TSQM = Treatment Satisfaction Questionnaire for Medication; UC = urothelial carcinoma; UTUC = upper tract urothelial carcinoma; w = week(s); W = visit week; WOCBP = women of childbearing potential.

[a] The Screening Period is up to 35 days for all patients. Screening procedures are to provide evidence of LG NMIBC and no evidence of HG disease. Enrollment should occur after Screening evaluations are completed and it is confirmed that the patient qualifies for the study. Every effort should be made to minimize the time interval between diagnosis and treatment.

[b] Patients who have a CR at the 3-month Visit will enter the Follow-up Period of the study. Patients who have an NCR at the 3-month Visit will undergo investigator designated SoC and have a separate EOS Visit performed.

[c] During the Follow-up Period, 3-month CR patients will return to the clinic every 3 months for evaluation of response. Patients will remain on study until disease recurrence, disease progression, death, or the last patient completes 12 months of follow-up (ie, 12 months after the 3-month Visit), whichever occurs first.

[d] Patients who discontinue from the study should have an EOS Visit performed. For 3-month CR patients who have a disease recurrence or progression during the Follow-up Period, an additional EOS Visit is not required (ie, the visit at which recurrence or progression is identified will serve as the patient's EOS assessments).

[e] Windows are provided to accommodate patient logistics in scheduling. Treatment instillations should occur 6 to10 days apart. Every effort should be made to minimize the time interval between diagnosis and Day 1 (the interval from end of Screening to first instillation should be ≤ 7 days).

[f] Obtain written informed consent before any study-related procedures are performed.

[g] Any past therapy (eg, pharmacological or surgical interventions) related to UC will be recorded during Screening.

[h] A general physical examination will be performed at the Screening Visit by licensed personnel at the investigative site. Additional general physical examinations may be performed during the study if clinically indicated.

[i] The urological examination should be performed before cystoscopy at the Screening Visit and before study treatment is administered at treatment visits. Additional urological examinations may be performed during the study if clinically indicated. Any clinically relevant changes in urological examinations will be recorded on the AE sections of the eCRF.

[j] Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.

[k] Dipstick on-site (all visits); central laboratory urinalysis with culture and sensitivity when requested by the site due to abnormal local laboratory results.

[l] Urine or serum pregnancy test (results assessed locally). Starting at Month 2, WOCBP will be tested for pregnancy once a month for up to 6 months after the last dose of study treatment. Pregnancy testing will be performed on-site at the 3-month Visit and 6-month Visit, and at the patient's home before the planned telephone contacts at Months 2, 4, 5, and 7. WOCBP will be sent home with pregnancy kits at appropriate time points and instructed to take one before each of the planned telephone contacts, during which the patient will inform the site of the pregnancy test results.

[m] CT urogram, retrograde pyelogram, or MRI (if other tests are contraindicated) to rule out UTUC (acceptable if performed within 6 months before Screening Visit) (results assessed locally).

[n] Cystoscopy and single representative cold cup biopsy to confirm LG tumor will be performed only if not already performed within 8 weeks before Screening Visit. If, in the investigator's assessment, tumors present on cystoscopy are sufficiently heterogenous in presentation such that 1 biopsy is not adequate, more than 1 biopsy sample can be taken. This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of the tumor is not to be performed. Residual tumor must be present (and tumor burden documented) after biopsy and before instillation of study treatment.

[o] No cytology is needed if results from a prior cytology within 8 weeks before Screening are available.

[p] The QLQ-C30 and TSQM should be administered before cystoscopy or administration of study treatment at relevant visits.

[q] Obtained within 12 months before Screening (if available).

[r] A subgroup of 9-12 patients who provide informed consent will have blood samples collected pre-dose and 0.5 (± 5 min), 1, 2, 3, 4, 5, and 6 hours (± 15 min at all time points) after the first instillation of UGN-103.

[s] Assessments should be performed as appropriate to the needs of the visit.

ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BCG	Bacillus Calmette-Guérin
CFR	Code of Federal Regulations
CI	Confidence interval
CIS	Carcinoma in situ
C_{max}	Maximum plasma concentration
CR	Complete response
CRR	Complete response rate
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of study
EU CTR	European Union Clinical Trials Regulation 536/2014
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GMP	Good Manufacturing Practice
HG	High grade
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Investigational product
IRB	Institutional Review Board

LG	Low grade
MedDRA	Medical Dictionary for Regulatory Activities
NCR	Non-complete response
NDD	No detectable disease
PI	Principal investigator
PK	Pharmacokinetic(s)
PQC	Product quality complaint
PRO	Patient-reported outcome
PT	Preferred term
q	Every
QC	Quality control
QLQ-C30	Quality of Life Questionnaire for Cancer Patients
QTL	Quality tolerance limit
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SMP	Study monitoring plan
SOA	Schedule of activities
SoC	Standard of care
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum plasma concentration
TSQM	Treatment Satisfaction Questionnaire for Medication
UC	Urothelial carcinoma
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
UTI	Urinary tract infection
UTUC	Upper tract urothelial carcinoma
WFI	Water for injection

2 INTRODUCTION

2.1 Background

UGN-102 (mitomycin) for intravesical solution is a reverse thermal gel formulation of mitomycin in Phase 3 development as a primary chemoablative treatment for patients with LG IR NMIBC.

UroGen is developing UGN-103, a reformulation of the mitomycin lyophilized powder in UGN-102, to simplify the reconstitution procedure and considerably shorten the manufacturing process. [redacted]

2.2 Study Rationale

[redacted] Instillation of mitomycin for intravesical solution into the urinary bladder aims to generate high concentrations of mitomycin at the site of the tumor and its immediate surroundings, with low systemic exposure. Therefore, UroGen proposes to conduct a clinical endpoint study in adult patients with LG IR NMIBC using the new formulation (UGN-103) [redacted]

[redacted]

[redacted]

2.3 Benefit-Risk Assessment

Refer to the UGN-102/UGN-103 Investigator's Brochure (IB) for more details on the benefit-risk profile of mitomycin for intravesical solution in patients with LG IR NMIBC.

2.3.1 Risk Assessment

Cystitis and Lower Urinary Tract Symptoms

Cystitis and other lower urinary tract symptoms may develop. These symptoms are well known in relation to standard mitomycin instillations and are not specific to mitomycin for intravesical solution. Urine tests, including urinalysis and urine culture as indicated, will be checked regularly during the study to monitor for potential UTI. Any signs and/or symptoms of UTI will be treated by the investigator according to local practice.

Toxicity Associated with Systemic Absorption/Local Irritation

Bladder toxicity and rarely bone marrow toxicity (thrombocytopenia and leukopenia) are considered possible risks for patients when mitomycin is administered topically. Complete blood count and renal and liver function tests will be checked during the study (Table 4), and the investigator will follow any clinically significant abnormality until it is resolved, stabilized, or otherwise managed (Section 8.2.3).

Allergic Response to Mitomycin

Allergic reactions during mitomycin bladder instillations are well described and have been observed during previous studies with UGN-102. Toxicities were generally manageable by treating patients with antihistamine drugs before and after treatment, and with systemic steroids as needed. Signs of an allergic response will be closely monitored during the study and managed by the investigator according to local practice.

Instillation Procedure

The insertion of a urethral catheter requires manipulation of the urethra and bladder. Some pain and discomfort are expected given the intravesical route of administration.

Potential risks of urethral catheterization include catheter associated UTIs, soreness, bleeding, bruising, and kidney infections.

Patients will be monitored for AEs during and for at least 30 minutes after each study treatment instillation.

Coronavirus Disease 2019 (COVID-19)

The COVID-19 pandemic has caused patients with cancer to confront the competing risks of potential COVID-19 exposure and delay in effective cancer treatment. Due to limited data, there are no international guidelines to address the management of cancer patients in an infectious pandemic. Therefore, consideration of risk and benefit for active intervention in the cancer population must be individualized.

There are no temporary or permanent requirements in the study for additional tests or procedures due to the COVID-19 pandemic. Any additional local COVID-19 related procedures (eg, COVID-19 testing for patients to attend site visits or undergo procedures related to this study) may be implemented at the discretion of the investigator.

Patients may receive authorized COVID-19 vaccines while participating in the study, including those granted emergency use authorization, but cannot participate in any investigational COVID-19 vaccine or other trials within 30 days of enrollment or during study conduct.

2.3.2 Benefit Assessment

The potential advantages of instillation of mitomycin in hydrogel include:

- Extended exposure of drug for up to 6 hours (compared with 1.5 to 2 hours in standard instillation). Published literature indicates that duration of tumor exposure to chemotherapy is critical to its ablative response. Thus, the effectiveness of tumor ablation is increased by longer dwell times.
- The hydrogel protects mitomycin from being diluted by urine, which leads to longer stable chemotherapy concentration levels.

These characteristics of mitomycin for intravesical solution are expected to improve mitomycin treatment efficacy and provide an alternative mode of treatment for NMIBC, which may be simpler and potentially better tolerated than current treatment modalities.

2.3.3 Overall Benefit-Risk Conclusion

Overall, based on the efficacy and safety results observed to date, mitomycin for intravesical solution has a favorable benefit-risk profile that supports its continued development for treatment of LG IR NMIBC.

3 OBJECTIVES AND ENDPOINTS

Objective	Endpoint
Primary	
• To evaluate the tumor ablative effect of UGN-103, a novel formulation of UGN-102, in patients with LG NMIBC	• CRR, defined as the proportion of patients who achieved CR at the 3-month Visit (3 months after the first instillation of UGN-103) as determined by cystoscopy, for cause biopsy, and urine cytology
Secondary	
• To evaluate the durability of response with respect to DOR and DCR rate at scheduled disease assessment time points	• DOR in patients who achieved CR at the 3-month Visit, defined as the time from the date of evidence of CR at the 3-month Visit to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, or death due to any cause, whichever occurred first • DCR rate at scheduled disease assessment time points, defined as the proportion of patients who achieved CR at the 3-month Visit and maintained CR (ie, no detectable disease) up to that particular follow-up disease assessment
• To evaluate the safety and tolerability of UGN-103 in patients with LG NMIBC	• Safety and tolerability will be evaluated through the reporting of AEs, including SAEs and AESIs, and through standard clinical and laboratory tests (eg, hematology and chemistry, urinalysis, physical examination, and vital signs)
• To assess the PK profile of mitomycin in plasma in a subgroup of patients treated with UGN-103	• Concentration data and PK parameters (C_{max}, t_{max}, and AUC)
Exploratory	
• To assess the effect of UGN-103 on PRO measures including disease related quality of life and treatment satisfaction	• Changes from baseline in patient scores on the QLQ-C30 and TSQM questionnaires
• To identify mechanisms of sensitivity and/or resistance to UGN-103	• DNA, RNA and/or protein biomarkers in tumor tissue
• To evaluate preliminary responses following SoC treatment in patients who have an NCR at the 3-month Visit	• Number (%) of response outcomes evaluated at the first disease assessment visit after SoC

AE = adverse event; AESI = adverse event of special interest; AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; CR = complete response; CRR = complete response rate; DCR = durable complete response; DNA = deoxyribonucleic acid; DOR = duration of response; LG = low grade; NCR = non-complete response; NMIBC = non-muscle invasive bladder cancer; PK = pharmacokinetic(s); PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire for Cancer Patients; RNA = ribonucleic acid; SAE = serious adverse event; SoC = standard of care; t_{max} = time to maximum plasma concentration; TSQM = Treatment Satisfaction Questionnaire for Medication.

4 STUDY DESIGN

4.1 Overall Design

This Phase 3, single-arm, multicenter study will evaluate the efficacy and safety of UGN-103, a novel formulation of UGN-102, instilled in the urinary bladder of patients with LG NMIBC.

Patients who provide informed consent will undergo a Screening Visit to determine eligibility. The Screening Period is up to 35 days for all patients. Screening procedures are to provide evidence of LG NMIBC and no evidence of HG disease, and every effort should be made to minimize the time interval between diagnosis and treatment.

Eligible patients will be treated with UGN-103 once weekly for 6 weeks (a total of 6 doses).

Efficacy will be assessed by the CRR at the 3-month Visit (approximately 3 months after the first instillation). Response will be determined based on visual observation (white light cystoscopy), histopathology of any remaining or new lesions by central pathology lab (if applicable), and interpretation of urine cytology by central pathology lab. Any lesions or suspect tissue must be biopsied to evaluate for persistence of disease.

Patients who have a CR at the 3-month Visit, defined as having NDD in the bladder, will enter the Follow-up Period of the study. During the Follow-up Period, patients will return to the clinic every 3 months for evaluation of response. Patients will remain on study until disease recurrence, disease progression, death, or the last patient completes 12 months of follow-up (ie, 12 months after the 3-month Visit), whichever occurs first.

Patients who have an NCR at the 3-month Visit will undergo investigator designated SoC and have a separate EOS Visit performed. Details of the SoC (eg, treatment modality, use and type of anesthesia, outcome, associated AEs) will be documented and the EOS Visit will occur 3 months (± 1 week) after SoC treatment.

Safety will be evaluated based on review of AEs and changes in laboratory assessments, physical examinations, and vital signs. All safety data will be reviewed on an ongoing basis by the sponsor, including close review and follow up of any unexpected AE assessed as related to UGN-103 and qualified per National Cancer Institute CTCAE version 5.0 as Grade 3 or 4.

If an unscheduled visit is required during the study, assessments should be performed as appropriate to the needs of the visit.

4.2 Scientific Rationale for Study Design

[redacted]

[redacted]

4.3 Dose Justification

[redacted]

4.4 End of Study Definition

The end of study (EOS) is defined as the last patient's last visit.

EOS will be declared after the last patient (ie, the last enrolled patient who has not recurred, progressed, died, withdrawn consent, or been lost to follow-up) has completed 12 months of follow-up (ie, 12 months after the 3-month Visit), or when the study is closed by the sponsor.

Patients who discontinue from the study should have an EOS Visit performed (Section 7.2).

For 3-month CR patients who have a disease recurrence or progression during the Follow-up Period, an additional EOS Visit is not required (ie, the visit at which recurrence or progression is identified will serve as the patient's EOS assessments) (Section 7).

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Provide written informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Patient must be ≥ 18 years of age at the time of informed consent.
3. Patient who has LG NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening. Note: This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of the tumor is not to be performed. Residual tumor must be present and documented after biopsy and before instillation of study treatment.
4. History of at least 1 prior episode of NMIBC. Note: This refers to a previous episode(s) and not to the current episode for which the patient is being screened.
5. Has intermediate risk disease, defined as having 1 or 2 of the following:
   a. Presence of multiple tumors.
   b. Solitary tumor > 3 cm.
   c. Early or frequent recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis at the initial Screening Visit).

   Note: Patients with all 3 factors are considered high risk and are not eligible to participate.
6. Negative voiding cytology for HG disease within 8 weeks before Screening.
7. Has adequate organ and bone marrow function as determined by routine laboratory tests as below:
   - Leukocytes ≥ 3,000/μL (≥ 3×10^9/L).
   - Absolute neutrophil count ≥ 1,500/μL (≥ 1.5×10^9/L).
   - Platelets ≥ 100,000/μL (≥ 100×10^9/L).
   - Hemoglobin ≥ 9.0 g/dL.
   - Total bilirubin ≤ 1.5 × ULN.
   - AST and ALT ≤ 2.5 × ULN.
   - ALP ≤ 2.5 × ULN.

- eGFR $\geq$ 30 mL/min.

8. Has an anticipated life expectancy of at least the duration of the trial.

9. Both male and female patients:

   Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   a. Female partner of male patient:

      Willing to use 2 acceptable forms of effective contraception from enrollment through 6 months post treatment if the female partner is of childbearing potential (defined as premenopausal women who have not been sterilized).

      Acceptable methods of birth control which are considered to have a low failure rate (ie, less than 1% per year) when used consistently and correctly, such as implants, injectable, combined (estrogen/progesterone) oral contraceptives, intrauterine devices (only hormonal), condoms with spermicide, sexual abstinence* or vasectomized partner.

      * Sexual abstinence is defined as refraining from intercourse from enrollment through 6 months post treatment. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is NOT an acceptable method of contraception.

   b. Female patient:

      Willing to use 2 acceptable forms of effective contraception from enrollment through 6 months post treatment if the patient is of childbearing potential (defined as premenopausal women who have not been sterilized).

5.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. Received BCG treatment for UC within the previous 1 year.

2. History of HG bladder cancer (papillary or CIS) in the past 2 years.

3. Known allergy or sensitivity to any component of the study treatment (including excipients) (Section 6.1.1) that in the investigator's opinion cannot be readily managed.

4. Clinically significant urethral stricture that would preclude passage of a urethral catheter.

5. History of:

   a. Neurogenic bladder.

   b. Active urinary retention.

   c. Any other condition that would prohibit normal voiding.

6. Past or current muscle invasive bladder cancer (ie, T2, T3, T4) or metastatic UC.

7. Current tumor stage of T1.

8. Concurrent UTUC.

9. Evidence of active UTI that in the investigator's opinion cannot be treated and resolved prior to biopsy and/or administration of study treatment.

10. Is pregnant or breastfeeding.

11. Has an underlying substance abuse or psychiatric disorder such that, in the opinion of the investigator, the patient would be unable to comply with the protocol.

12. History of prior treatment with an intravesical chemotherapeutic agent in the past 2 years except for a single dose of chemotherapy immediately after any previous TURBT.

13. Has participated in a study with an investigational agent or device within 30 days of enrollment.

14. Has previously participated in a study in which they received UGN-102.

15. Has any other active malignancy requiring treatment with systemic anticancer therapy (eg, chemotherapy, immunotherapy, radiation therapy). Superficial cancers such as cutaneous basal cell or squamous cell carcinomas that can be treated locally are allowed.

16. Has any other clinically significant medical or surgical condition that in the investigator's opinion could compromise patient safety or the interpretation of study results.

17. Where applicable per country regulation, the patient must not be currently committed to an institution by virtue of an order issued by either judicial or administrative authorities.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the study but are not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. Rescreening of patients is permitted in this study.

5.5 Strategies for Recruitment and Retention

A sufficient number of patients will be screened to ensure that approximately 87 patients with LG IR NMIBC are enrolled in the study. Patients who discontinue may be replaced at the sponsor's discretion. The study will be conducted at approximately 55 investigative sites in the US and Europe that provide care to patients with bladder cancer.

6 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study patient according to the study protocol.

6.1 Study Treatment Administered

6.1.1 Study Treatment Description

[redacted] UGN-103 admixture is prepared in advance of use by the qualified location for drug preparation (typically, the pharmacy) according to the Instructions for Pharmacy. The UGN-103 single dose kit contains the components summarized in Table 1.

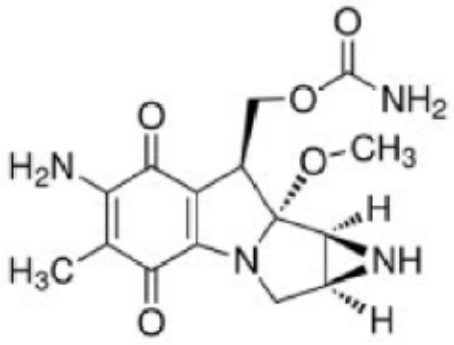
Table 1 UGN-103 Components

Component	Quantity per Single Dose Kit [a]	Function
Mitomycin for solution (vial)	80 mg	Active ingredient
Sterile hydrogel (vial)	60 mL	Vehicle
UGN-103 admixture labels	3	Admixture labels
100 mL vial	1	Empty vial for reconstitution
Instructions for Pharmacy	1	Instructions for admixture
Instructions for Administration	1	Instructions for instillation

[a] [redacted].

See Figure 1 for the chemical structure of mitomycin.

Figure 1 Structure of Mitomycin, USP



USP = United States Pharmacopeia.

Chemical name: 7-amino-9α-metho3xymitosane

Formula: $C_{15}H_{18}N_4O_5$

Molecular weight: 334.33 g/mol

CASRN: 50-07-7

The vials of 80 mg mitomycin for solution are manufactured for UroGen Pharma Ltd. by [redacted]

The contents of each mitomycin for solution vial are summarized in Table 2.

Table 2 Vial Composition of Mitomycin for Solution

Component	Quantity (mg per Vial)	Pharmaceutical Grade	Function
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]

NF = National Formulary; USP = United States Pharmacopeia.
[a] Solvent is removed during lyophilization.

The vials of 60 mL sterile hydrogel are manufactured for UroGen Pharma Ltd. [redacted]

The contents of each sterile hydrogel vial are a proprietary mixture of [redacted]

[redacted]

6.1.2 Preparation and Administration Ancillaries

Ancillaries used to prepare and administer the study treatment are detailed in the Instructions for Pharmacy and Instructions for Administration.

6.1.3 Clinical Nurse Educators

This study will contract clinical nurse educators to train pharmacy personnel on study treatment preparation and site personnel on the UGN-103 instillation procedure. The role of the clinical nurse educator in the current study will include, but may not be limited to:

- Conduct training on UGN-103 instillation procedures for the PI, sub-investigator(s), and other relevant personnel before the first study treatment administration.
- Be present for training purposes during the first study treatment administration, if allowed by the site.
- Conduct training for pharmacy personnel on UGN-103 study treatment preparation according to the Instructions for Pharmacy.
- Following training, attend the first pharmacy preparation, if allowed by the pharmacy.

6.1.4 Administration and Dosing

Patients will receive 6 once weekly intravesical instillations of study treatment. Patients should be monitored for AEs during and for at least 30 minutes after each study treatment instillation.

Mitomycin Concentration	UGN-103 Volume	Route of Administration [a]
[redacted] mg/mL	[redacted] mL	Local administration into the bladder

[a] Refer to UGN-103 Instructions for Administration for detailed instillation instructions.

The PI or sub-investigator must perform the first instillation for the first patient at his/her site. Subsequent instillations may be performed by an appropriately trained and delegated site staff member (as per site standard practice for instillations), provided an appropriately trained study physician is on-site during the procedure.

Study treatment administration will be documented in the patient file, electronic case report forms (eCRFs), and in the Drug Administration Records.

Hospitalization is not a requirement for this study. Patients will be admitted to and discharged from the hospital at the discretion of the investigator. UGN-103 instillations are expected to occur at the study site on an ambulatory basis.

6.1.5 Criteria for Temporarily Delaying Administration of Study Treatment

If at any time during the study the investigator identifies clinically significant myelosuppression, evidence of an active UTI, or any other significant clinical event or laboratory derangements that meet the pre-defined parameters (Section 8.2.3.1), treatment may be postponed for up to 4 weeks until the clinical event resolves and/or laboratory values improve.

6.1.6 Treatment of Overdose

Not applicable.

6.2 UGN-103 Single Dose Kit Handling, Storage, and Accountability

6.2.1 Acquisition and Accountability

The UGN-103 single dose kit is assembled for UroGen Pharma Ltd. by [redacted]
All clinical supplies will be packaged and labeled in compliance with GMP guidelines. The shipment process should comply with the rules of Good Distribution Practices. Before shipment of clinical supplies, the sponsor or sponsor's designee should notify the PI regarding the anticipated date of arrival at the hospital/clinic pharmacy. The investigational product (IP) will be sent to the site only after receipt of study approval from the IRB or regulatory agency, as applicable. The shipment will be sent to the investigator's authorized study personnel at the site's pharmacy.

All dispensed study treatments will be appropriately documented to ensure proper handling in case of emergency.

[redacted]

If, upon arrival, the IP supplies appear to be damaged or the temperature was above or below the specified limit during shipment, the clinical site pharmacy will contact and report the issue immediately according to the product quality complaint (PQC) procedure described in Section 6.2.5. The impacted IP must be marked "not for use" and quarantined during investigation until a decision has been made regarding the drug's validity.

Each shipment of IP supplies for the study will contain at minimum, a shipment form describing the content of shipment. This form will assist in maintaining current and accurate inventory records. When a shipment is received, the appropriate site personnel will acknowledge receipt of the IP supply.

Unused UGN-103 must be available for verification by the sponsor's site monitor during on-site monitoring visits, if allowed by the local regulations. Unused or expired UGN-103 returned to the sponsor must be documented on the drug return form.

The investigator agrees to neither dispense the study treatment from, nor store it at, any site other than the site agreed upon with the sponsor.

Unusable UGN-103 single dose kits will be marked "not for use" in pen over the label and stored separately from usable UGN-103 single dose kits.

Replacement UGN-103 will be supplied after a request for additional supplies has been issued to the sponsor's designee.

Following completion of drug accountability by the clinical research associate, used study treatment vials should be discarded locally according to local institution guidelines for cytotoxic waste destruction. Discarding/destruction of the used UGN-103 admixture vials must be documented in the drug disposal form.

6.2.2 Formulation, Appearance, Packaging, and Labeling

The formulation of the study treatment and the contents of UGN-103 are described in Section 6.1.1. All clinical supplies will be packaged and labeled in compliance with GMP guidelines. All information regarding study treatment provided will be appropriately documented (eg, batch records, certificate of analysis). The original product packaging will be used in the study (UroGen Pharma Ltd., Israel).

6.2.3 Product Storage and Stability

[redacted]

The clinical supplies storage area at the investigative site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range as specified on the label. Documentation of temperature monitoring should be maintained and available for review.

6.2.4 Admixture

[redacted] The elapsed cooling time must be documented, which includes the length of time at room temperature, as well as length of time in ice.

6.2.5 Product Quality Complaint Handling

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, or reliability of a product, including its labeling or packaging integrity. In such cases, and also in cases of temperature deviation, either during transport, storage, or preparation at the pharmacy the investigator is responsible for notifying the sponsor about the defect/temperature deviation. Any PQCs must be reported to the sponsor or sponsor's designee using:

[redacted]

Reporting must be done upon first awareness, and the site should await the sponsor's decision regarding the drug's validity before drug dispensing.

If the PQC is associated with an SAE, the investigational staff must report the PQC to the sponsor or sponsor's designee as described above and the SAE(s) must be reported according to Section 8.3.6 (Serious Adverse Event Reporting). The affected study products must be quarantined and marked "not for use" during investigation until a decision has been made regarding the drug's usability.

PQCs may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from clinical studies are crucial for the protection of patients, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

6.3 Measures to Minimize Bias

This is an open-label, single-arm study; potential bias will be reduced by the following measures:

- Objective assessments will be used to determine diagnosis and evaluate response at each time point, including:
  - Direct visualization of the bladder leveraging standard urologic practices (white light cystoscopy).
  - Histopathology of any remaining or new lesions by central pathology lab.
  - Interpretation of urine cytology by central pathology lab.
- Sites will be trained to evaluate responses following standard practices, which have been prospectively defined in Section 8.1.2 and Appendix 1 (Guidance on Evaluation of Response).

6.4 Study Treatment Compliance

The study treatment will be administered at the investigative site by properly trained and qualified health care personnel. Each drug administration (including date, time, volume administered) will be documented in the patient's file and eCRF.

6.5 Prior/Concomitant and Prohibited Therapy

Only authorized concomitant medications may be used in the study. Any concomitant medication (including prescription or over-the-counter medications) that the patient is receiving at the time of enrollment or receives during the study and any prior therapies (eg, pharmacological or surgical interventions) related to UC must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Route of administration

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

Prohibited concomitant medications and procedures include:

- Systemic anticancer therapy (eg, chemotherapy, immunotherapy, radiation therapy)
- Intravesical chemotherapy
- Intravesical immunotherapy
- Surgical resection of bladder tumors (eg, TURBT, fulguration)

  Note: Surgical resection of bladder tumors is permitted at the time of suspected NCR (3-month Visit) or recurrence/progression (Follow-up Period) based on investigator medical judgment and standard practice at the study site.

In cases of symptomatic UTI, the patient will be treated with a course of antibiotics, and study treatment will be postponed until resolution. In the case of asymptomatic bacteriuria, the use of prophylactic antibiotics and postponement of study treatment is left to the discretion of the PI or qualified designee.

The investigator should contact the medical monitor if there are any questions regarding prior or concomitant therapy.

6.5.1 Rescue Medicine

No rescue therapy is planned for this study.

6.6 Dose Modification

Not applicable.

6.7 Continued Access to Study Treatment After the End of the Study

Not applicable.

7 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

3-month CR patients who have a disease recurrence or progression during the Follow-up Period, or who are still in follow-up when EOS is declared (Section 4.4), will be considered to have completed the study. For 3-month CR patients who have a disease recurrence or progression during the Follow-up Period, an additional EOS Visit is not required (ie, the visit at which recurrence or progression is identified will serve as the patient's EOS assessments).

3-month NCR patients will be considered to have completed the study following the EOS Visit 3 months (± 1 week) after SoC treatment.

Once a patient has completed or been discontinued from the study, further treatment options will be at the discretion of the investigator.

7.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not mean discontinuation from the study. Patients who discontinue study treatment should remain in the study and all relevant visits and procedures should continue as indicated by the study protocol.

If a clinically significant finding is identified after enrollment (including, but not limited to, changes from baseline), the investigator or qualified designee will determine if any change in patient management is needed. Any new clinically relevant finding will be reported as an AE.

7.1.1 Temporary Withholding of Study Treatment

If at any time during the study the investigator identifies clinically significant myelosuppression, evidence of an active UTI, or any other significant clinical event or laboratory derangements that meet the pre-defined parameters (Section 8.2.3.1), treatment may be postponed for up to 4 weeks until the clinical event resolves and/or laboratory values improve.

7.1.2 Rechallenge

There will be no change in dose for patients who restart study treatment after temporary withholding (Section 7.1.1).

7.2 Patient Discontinuation/Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or compliance reasons.

Reasons for discontinuation from the study include:

- Withdrawal of consent
- Lost to follow-up
- Investigator's discretion
- Protocol non-compliance
- Pregnancy
- AE leading to study discontinuation
- Death

The reason for patient discontinuation or withdrawal from the study will be recorded in the eCRF.

Patients who discontinue from the study should have an EOS Visit performed. See the Schedule of Activities (SOA) (Section 1.3) for the procedures to be performed and the data to be collected at the time of study discontinuation. The patient will be permanently discontinued from both study treatment and the study at that time.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she fails to return for 2 sequential scheduled visits and is unable to be contacted by the investigative site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site will attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain if the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's study file.

Should the patient continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SOA (Section 1.3). Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SOA, is essential and required for study conduct.

All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a Screening log to record details of all patients screened and to confirm eligibility or record reasons for screen failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SOA.

If an unscheduled visit is required during the study, assessments should be performed as appropriate to the needs of the visit.

8.1 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SOA (Section 1.3).

8.1.1 Measurements for Evaluation of Response at the 3-month Visit and Follow-up Visits

Assessment of response will be based on the following:

- Visual observation (white light cystoscopy)
- Histopathology of any remaining/new lesions by central pathology lab, if applicable
- Voiding urine cytology by central pathology lab

8.1.2 Evaluation of Response at the 3-month Visit and Follow-up Visits (Disease Assessment)

Patient response at the 3-month Visit and follow-up visits will be determined according to the following criteria. Refer to Appendix 1 (Guidance on Evaluation of Response) for more details.

- **CR:** A patient will be considered to have a CR if there is NDD in the bladder. To determine NDD, the following conditions should be fulfilled:
  - If visual assessment indicates no remaining tumors and urine cytology is not consistent with the presence of UC, the patient has NDD and CR.
  - If any remaining lesions appear, even if they appear necrotic, the physician should biopsy the lesion(s). If histopathology is negative, the patient should be classified as

CR; if positive for cancer, the patient should be classified as NCR (3-month Visit) or recurrence (follow-up visits).

- **NCR:** A patient will be considered to have an NCR if there is evidence of the disease under study:
  - If tumors are still visible, all remaining lesions should be biopsied for histopathology and viability assessment. If histopathology still indicates cancer, the patient should be classified as NCR. Note: Biopsy results showing papillary urothelial neoplasm of low malignant potential (PUNLMP) are not considered cancer and in such cases the patient should be classified as CR.

- **Recurrence:** Patients who have a CR at the 3-month Visit will enter the Follow-up Period of the study. During the Follow-up Period, patients will return to the clinic every 3 months for evaluation of response. Patients will remain on study until disease recurrence, disease progression, death, or the last patient completes 12 months of follow-up (ie, 12 months after the 3-month Visit), whichever occurs first. The criteria for determining recurrence is similar to that of NCR.

- **If evidence of disease is identified,** patients will be staged according to the Tumor-Node-Metastases classification and graded according to the 2004 World Health Organization classification of tumors. Any noted progression of tumor in terms of transition to HG (central lab), muscle invasion (central lab), or distant disease (local assessment) will be documented by the site in the eCRF. See Section 8.1.3 for more details on assessment of tumor progression.

- In the rare event that the bladder is free of tumor endoscopically, but the cytology is consistent with UC, the urine cytology should be repeated. Note: Atypical cells identified on urine cytology are not consistent with LG NMIBC or malignancy in general, and abnormal urine cytology findings require clinical context to support interpretation, particularly in the presence of a normal cystoscopy.
  - If the repeat urine cytology is consistent with UC, the investigator is required to exclude UTUC and occult carcinoma of the bladder or urethra.
  - If UTUC is confirmed, the patient will be considered a CR for LG NMIBC. If UTUC is not confirmed, the investigator must perform random bladder biopsies (RBB) to examine the following 6 bladder mucosal sites: bladder floor, right wall, left wall, dome, posterior wall, and prostatic urethra (in males) or bladder neck (in females).
  - If histopathology is negative, the patient should be classified as CR; if positive for cancer, the patient should be classified as NCR (3-month Visit) or recurrence (follow-up visits).

- **Indeterminate**: A patient response will be indeterminate if the criteria for determining either CR or NCR/recurrence is not fulfilled due to incomplete or missed assessment. Questionable interpretations must be resolved and not be assessed as indeterminate.

In case the evaluation of response is "indeterminate" at the 3-month Visit or a follow-up visit, sites must perform the required procedures as soon as possible in order to have an adequate response evaluation.

8.1.3 Assessment of Tumor Progression

The overall risk of progression for patients with LG papillary NMIBC at intermediate risk of recurrence ranges from approximately 1%-5% at 1 and 5 years (Babjuk et al, 2019).

Diagnosis of bladder cancer at the 3-month Visit or subsequent follow-up visits with an increase in stage or grade compared to baseline will be recorded in the evaluation of response, and the overall incidence will be compared with that reported in the literature. Refer to Section 7 for details on study completion and patient discontinuation/withdrawal.

8.1.4 Assessment of Tumor Recurrence

Patients who have a CR at the 3-month Visit will enter the Follow-up Period of the study.

Starting with the first follow-up visit (Month 6) and continuing at subsequent follow-up visits, information regarding disease status based on cystoscopy, for cause biopsy, and urine cytology should be recorded (Section 8.1.2 and Appendix 1). If a patient is determined to have disease recurrence or persistence, complete documentation should be obtained. Refer to Section 7 for details on study completion and patient discontinuation/withdrawal.

8.1.5 Pathological Evaluation

Biopsies and urine cytology specimens obtained at Screening or any other visit should be evaluated by the central laboratory (pathologist). Pathology reports from the central laboratory will be provided to investigators. Details on the collection, processing, storage, and shipment of samples to the central laboratory are provided in the Laboratory Manual. Remaining biopsy samples may be used for exploratory correlative studies (Section 8.8).

8.2 Safety Assessments

The safety of study treatment will be assessed by the following:

- Evaluation of AEs (frequency, seriousness, severity, and type) including AEs of special interest (AESIs)
- Changes from baseline in laboratory values and incidence of measurements defined as potentially clinically significant
- Clinically meaningful changes in physical examination findings including vital signs

Planned time points for all safety assessments are provided in the SOA (Section 1.3).

8.2.1 Physical Examinations

A general physical examination and/or urological examination will be performed at the visits specified in Section 1.3. The examinations to be performed are summarized in Table 3. Additional general physical examinations or urological examinations may be performed during the study if clinically indicated.

Height and body weight will be measured during Screening.

Table 3 Physical Examinations

General Physical Examination	Urological Examination [a]
General appearance	Urethral meatus
Cardiovascular system	Perineal skin and mucus membranes
Respiratory system	Scrotum and testes (in male patients)
HEENT (head, eyes, ears, nose, and throat) and neck	Lymphadenopathy
Abdomen	
Extremities	
Neurologic system	
Skin	

[a] The urological examination should be performed before cystoscopy at the Screening Visit and before study treatment is administered at treatment visits.

8.2.2 Vital Signs

The following vital signs parameters will be measured:

- Body temperature
- Pulse rate
- Respiratory rate
- Blood pressure

Blood pressure and pulse rate measurements will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Clinical Safety Laboratory Assessments

Samples for hematology and serum chemistry assessments will be collected according to the SOA in Section 1.3 and tested at the central laboratory. The parameters to be analyzed are summarized in Table 4. All protocol required laboratory tests must be conducted in accordance with the Laboratory Manual and the SOA. No samples will be used for non-study related purposes.

Table 4 Safety Laboratory Assessments

Liver Function Tests	Kidney Function Tests	Hematology Tests
AST	Creatinine	Complete blood count, including red blood cell indices and white blood cell differential
ALT	Blood urea nitrogen	
GGT	Uric acid	Platelet count
ALP	Sodium	
Total bilirubin	Potassium	
Direct bilirubin	Bicarbonate	
Albumin	Chloride	
Total protein	eGFR (calculated by central lab)	

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyl-transferase.
Note: Laboratory samples will be kept according to storage requirements stated in the Laboratory Manual until shipped to the central laboratory for analysis.

The investigator must review the laboratory report from previous visit(s), document this review, and record any laboratory abnormalities as clinically significant or not clinically significant. Any clinically significant changes should have a corresponding AE reported. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study (eg, in case of temporary discontinuation) or within 4 weeks after the last administered dose of study treatment (ie, in case of permanent discontinuation) should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If any clinically significant or other values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

A central laboratory will be used in this study, except for the pregnancy test (either urine or serum) and urinalysis (dipstick), which are performed at the site or locally. Urinalysis with culture and sensitivity will be performed by the central laboratory when requested by the site due to abnormal local laboratory results.

During the study, circumstances may arise that necessitate use of the site's local laboratory for protocol specified laboratory tests (eg, when necessary for rapid reporting, AE monitoring, or if a sample sent to the central laboratory is delayed, damaged, or lost). These results must be recorded in the eCRF. If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the investigator (eg, AE), then the results must be recorded.

Local laboratory reports are expected to be filed with the patient source documents, but investigators must defer to central laboratory results when contemporaneous reports differ.

8.2.3.1 Other Significant Laboratory Derangements

If at any time during the study the investigator identifies clinically significant myelosuppression, evidence of an active UTI, or any other significant clinical event or laboratory derangements defined by the parameters below, treatment may be postponed for up to 4 weeks until the clinical event resolves and/or laboratory values improve:

- Absolute neutrophil count $\leq$ 1,000/µL ($\leq 1.0 \times 10^9$/L).
- Platelets $\leq$ 80,000/µL ($\leq 80 \times 10^9$/L).
- AST and/or ALT $\geq 5 \times$ ULN.
- Laboratory evidence of active UTI.

The investigator should contact the medical monitor if the clinical event does not resolve and/or the laboratory values do not improve after 4 weeks.

8.2.3.2 Urinalysis

Samples will be collected for urinalysis, including culture and sensitivity (if suggestive of infection) at Screening and when otherwise clinically indicated, at the visits specified in Section 1.3.

8.2.3.3 Pregnancy Testing

A urine or serum pregnancy test (results assessed locally) will be conducted in female patients of childbearing potential at the visits specified in Section 1.3. A female is considered of childbearing potential unless:

- At least 12 months have elapsed since the last menstrual bleeding; or
- She is without a uterus and/or both ovaries; or
- She has been surgically sterile for at least 6 months before study treatment administration.

Pregnancy testing will be performed on-site at in-person visits, and at the patient's home before planned telephone contact visits. Patients will be sent home with pregnancy kits at appropriate time points and instructed to take one before each of the planned telephone contacts, during which the patient will inform the site of the pregnancy test results.

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

AEs and SAEs are defined in Section 8.3.1. AEs and SAEs will be collected from the signing of the ICF (Section 8.3.2).

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events according to instructions in Section 8.3.2 and remain responsible for following up all applicable AEs including those that are serious, considered related to study treatment or study procedures, or that caused the patient to discontinue study treatment or participation in the study (Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 8.3.1, Section 8.3.5, and Section 8.3.6.

8.3.1 Adverse Events and Serious Adverse Events

8.3.1.1 Definition of Adverse Event

An AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 [a]; EU CTR 536/2014). An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product ("Note for Guidance on Good Clinical Practice" CPMP/ICH/135/95).

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, serum chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments.

However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Any patient who reports an AE shall be examined by a doctor as soon as possible, making whatever intervention is necessary for the safety and well-being of the patient. All anomalies shall be monitored through to the patient's recovery or clinical stabilization. Collected reportable AEs must be recorded in the eCRF using CTCAE version 5.0 (CTCAE, 2017) to avoid the use of vague, ambiguous, or colloquial expressions. The investigator shall evaluate all collected reportable AEs in terms of severity and their relationship with the product being tested, indicating the test results and the measures to be taken.

8.3.1.2 Definition of Serious Adverse Event

An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the

event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

8.3.1.3 Classification of an Adverse Event

8.3.1.3.1 Severity of Event

The severity (intensity) of an AE is to be graded by the investigator according to CTCAE version 5.0 (CTCAE, 2017) definitions of severity, as follows:

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

8.3.1.3.2 Relationship to Study Treatment (Assessment of Causality)

All AE/SAEs must have their relationship to study treatment/interventions and study procedures assessed by the clinician who examined and evaluated the patient based on temporal relationship and his/her clinical judgment. In a clinical study, the study product must always be suspect. Investigators will be asked to grade each AE/SAE as either related (a reasonable possibility of a relationship) or unrelated.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator is instructed to also consult the IB in his/her assessment.

For each collected reportable AE/SAE, the investigator is instructed to document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor's designee (via electronic data capture [EDC]/eCRF transmission). However, it is very important that the investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to the sponsor's designee (via EDC/eCRF transmission).

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.3.1.3.3 Expectedness

The sponsor will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment.

An unexpected adverse drug reaction is any noxious and unintended response that is related to the administration of an IP that has not been reported as expected in the IB (reference safety information for this study), either from previous clinical studies or nonclinical studies.

A suspected unexpected serious adverse reaction (SUSAR) is any unexpected adverse drug reaction that at any dose also meets the criteria for SAE.

8.3.2 Time Period and Frequency for Collecting AE and SAE Information

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor.

All AEs (including local and systemic reactions not meeting the criteria for SAEs) and SAEs will be collected from the signing of the ICF to the 6-month Visit. After the 6-month Visit, all SAEs (regardless of causality) and non-serious AEs assessed as related to study treatment or study procedures should be collected until the EOS at the time points specified in the SOA (Section 1.3). Information will be captured on the appropriate eCRF including event description, date of onset, clinician's assessment of severity and relationship to study treatment and study procedure, and date of resolution/stabilization of the event. All collected reportable AEs occurring while on study must be documented appropriately. All collected AEs will be followed to adequate resolution/stabilization.

If the study patient's condition deteriorates at any time during the study, it will be recorded as an AE. AEs reported from the time of study treatment administration will be considered as treatment-emergent AEs (TEAEs).

AEs characterized as intermittent require documentation of onset and duration of each episode.

At study visits or telephone contacts specified in the SOA (Section 1.3), the investigator and/or designee should inquire about the occurrence of AE/SAEs since the last visit/telephone contact. The investigator or designated investigational staff member should record the start date of all collected reportable events. Events will be followed for outcome information until resolution or stabilization and the dates of outcome must be recorded.

All SAEs are to be recorded and reported to the sponsor immediately and under no circumstance should this exceed 24 hours. The investigator should submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor within 24 hours.

8.3.3 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.4 Follow-up of AEs and SAEs

After the initial collected AE/SAE report, the investigator and/or designee is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (Section 7.3). Further information on follow-up procedures is provided in Section 8.3.6.

8.3.5 Regulatory Reporting Requirements for SAEs

Each patient must be given a patient card containing details of the contact person at the site he/she should contact in case any unusual or serious signs or symptoms develop after treatment. Where required, patients will be examined at the center and will be clinically monitored until they recover.

Expedited reporting to the sponsor is required in the following conditions:

1. Any SAE and follow-up SAE report, if required
2. Death of study patient
3. Pregnancy and outcome of the pregnancy

The investigator must inform the sponsor/sponsor's designee about the above by completing and submitting the SAE/Death eCRF or Pregnancy Report Form within 24 hours after its occurrence first came to his/her knowledge.

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study treatment under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to regulatory authorities (including reporting of SUSARs to the EudraVigilance database), IRBs/IECs, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it in the Investigator File and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared by the sponsor for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.6 Serious Adverse Event Reporting

The investigator will immediately report to the sponsor any SAE, whether or not considered related to study treatment or study procedure, including those listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the study treatment or study procedure caused the event.

All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the patient is stable. Other supporting documentation of the event may be requested by the sponsor or sponsor's designee and should be provided as soon as possible.

The sponsor will be responsible for notifying relevant health authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify relevant health authorities and all participating investigators in an investigational product safety report of potential serious risks, from clinical studies or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.3.6.1 SAE Reporting Instructions

The investigator must inform the sponsor within 24 hours of becoming aware of an SAE (or updated SAE information) by completing and submitting the SAE/Death eCRF or Pregnancy Report Form.

It is not acceptable for the investigator to send photocopies of the patient's medical records to the sponsor or designee in lieu of completion of the SAE/Death eCRF or Pregnancy Report Form.

There may be instances when copies of medical records for certain cases are requested by regulatory or other agencies. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE when the EDC tool has been taken offline or is unavailable, then the site can report this information on a paper SAE form to the sponsor (or designee) or medical monitor by email or telephone within 24 hours.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.

The following is the contact information for SAE reporting:

- Email: [redacted]
- Telephone (UroGen AE Call Center): [redacted]

8.3.7 Pregnancy

Details of all pregnancies in female patients and female partners of male patients will be collected from the start of study treatment to the 6-month Visit. The investigator shall immediately discontinue study treatment (if applicable) and ensure expedited reporting of the event within 24 hours (Section 8.3.5). The patient/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the patient/pregnant female partner and the neonate, and the information will be forwarded to the sponsor.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the investigator will be reported to the sponsor as described in Section 8.3.5. While the investigator is not obligated to actively seek this information in former study patients/pregnant female partners, he or she may learn of an SAE through spontaneous reporting.

8.3.8 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.3.9 Adverse Events of Special Interest

In this study, AESIs will be monitored on an ongoing basis through a regular review of AE listings. There are no requirements for the investigator to make determinations of AESIs and investigators are to report all AEs in a consistent manner as described in Section 8.3.2.

[redacted], investigators will document the clinical condition of the bladder at visits when cystoscopy is performed (Section 1.3). Clinically significant changes to the condition of the bladder visualized during cystoscopy (eg, presence of pathological changes or gross abnormalities other than tumor) will be documented in the eCRF and should have a corresponding AE reported.

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

8.4 Patient-Reported Outcome Measures

Planned time points for PRO measures are provided in the SOA (Section 1.3). PRO measures should be administered before cystoscopy or administration of study treatment at relevant visits.

8.4.1 Quality of Life Questionnaire for Cancer Patients (QLQ-C30)

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for Cancer Patients (QLQ-C30) is one of the most widely used cancer-specific questionnaires worldwide (Nolte et al, 2019). It assesses a variety of side effects that are common during cancer treatment, including fatigue, pain, nausea and vomiting, dyspnea, insomnia, appetite loss, constipation and diarrhea, mood, cognition, physical functioning, role functioning (daily activities), and a global health status scale. The recall period for the items is the past week.

The QLQ-C30 is provided in Appendix 2.

8.4.2 Treatment Satisfaction Questionnaire for Medication (TSQM)

The Treatment Satisfaction Questionnaire for Medication (TSQM) is a general measure of patient satisfaction with medication. It has been shown that the TSQM is a good predictor of patient medication adherence across different types of medication and patient populations. The scale was developed in 2004 and contains 4 domains: efficacy, side effects, convenience, and global satisfaction. The objective of TSQM measurement in this study is to assess patient satisfaction with UGN-103 across these 4 domains.

The TSQM is provided in Appendix 3.

8.5 Pharmacokinetics

Patients at select sites will be asked to participate in blood sample collection for PK analysis. A subgroup of 9-12 patients who provide informed consent will have blood samples collected pre-dose and 0.5 (± 5 min), 1, 2, 3, 4, 5, and 6 hours (± 15 min at all time points) after the first instillation of UGN-103. Concentration data and PK parameters (eg, C_{max}, time to maximum plasma concentration [t_{max}], and area under the concentration-time curve [AUC]) will be summarized using descriptive statistics. The PK parameters obtained, specifically the C_{max}, will be compared to the mitomycin plasma concentration known to be associated with myelosuppression (400 ng/mL). No samples will be used for non-study related purposes.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Tumor tissue from an archival biopsy obtained within 12 months before screening (if available) and remaining tumor tissue from on study visits may be used for correlative studies to understand mechanisms of sensitivity and/or resistance to UGN-103. These studies may include,

but are not limited to, molecular alterations to deoxyribonucleic acid (DNA) and gene or protein expression patterns. Tumor tissue samples, including formalin fixed embedded tissues, blocks, or slides, will be stored at a qualified central repository for up to 10 years or until use. All samples will be pseudonymized and the code list held by the sponsor and/or its designee. Samples will be analyzed in the US or EU by one or more third parties and response data may be shared with these third parties for correlative analysis. At the completion of these studies any remaining tumor tissue samples will be destroyed. Details on the handling and processing of samples for this research are provided in the Laboratory Manual.

Consent to provide tumor tissue for correlative studies is optional and not required for entry into the study.

8.9 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

It is planned that the data from all centers participating in the study will be combined to ensure that an adequate number of patients are available for analysis.

9.1 Statistical Hypotheses

No formal hypothesis will be tested for the confirmation of efficacy. The hypothesis described in Section 9.2 is provided only for the justification of sample size.

[redacted]

9.2 Sample Size Determination

The primary endpoint of this study is CRR at the 3-month Visit.

Approximately 87 patients will be enrolled. The sample size calculation is based on the level of precision of the estimated CRR. For an observed CRR of 60.9%, the 95% exact CI is (49.8%, 71.2%) with 87 patients. Assuming a CRR of 60% in the study as compared to 45%, using a binomial exact test, the power is 79.2% with 87 patients to demonstrate statistical significance at a 1-sided alpha of 0.025.

Table 5 shows the 95% CI for a range of possible response rates based on 87 patients, and Table 6 shows the power under different assumptions of true 3-month CRR.

Table 5 Sample Size Sensitivity

Sample Size	Number of Responders (Observed 3-month CRR)	95% Exact 2-sided CI
87	50 (57.5%)	(46.4, 68.0)
	53 (60.9%)	(49.8, 71.2)
	57 (65.5%)	(54.6, 75.4)

CI = confidence interval; CRR = complete response rate.

Table 6 Statistical Power Scenarios

Sample Size	True 3-month CRR	Probability That the Lower Bound of a 2-sided 95% Exact CI Will Exclude 0.45
87	0.65	0.963
	0.64	0.944
	0.63	0.918
	0.62	0.885
	0.61	0.842
	0.60	0.792
	0.59	0.733
	0.58	0.666
	0.57	0.595
	0.56	0.521
	0.55	0.446

CI = confidence interval; CRR = complete response rate.

9.3 Populations for Analyses

The following analysis sets are defined for the purposes of analyses:

Analysis Set	Description
Safety analysis set	The safety analysis set includes all patients who received any dose of UGN-103 and will serve as the primary population for efficacy and safety analyses.
PK analysis set	The PK analysis set includes patients in the safety analysis set who provide consent for PK samples and have at least 1 plasma sample for evaluation of PK properties of mitomycin.
CR at 3-month Visit analysis set (3-month_{CR})	The CR at 3-month Visit (3-month_{CR}) analysis set will consist of all patients from the safety analysis set who achieved CR at the 3-month Visit. The secondary endpoints DOR and DCR rate at specific time points will be analyzed using this analysis set.
NCR at 3-month Visit analysis set (3-month_{NCR})	The NCR at 3-month Visit (3-month_{NCR}) analysis set will consist of all patients from the safety analysis set who were NCR at the 3-month Visit. The preliminary response of these patients following the SoC treatment will be analyzed using this analysis set.

CR = complete response; DCR = durable complete response; DOR = duration of response; NCR = non-complete response; PK = pharmacokinetic(s); SoC = standard of care.

9.4 Statistical Analyses

9.4.1 General Considerations

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated using descriptive statistics. For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency, and 95% CI for proportions using the exact approach. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation, coefficient of variation (if appropriate), median, minimum and maximum, percentiles, and 95% CI for means of variables as appropriate.

9.4.2 Primary Endpoint

The primary endpoint is CRR, defined as the proportion of patients who achieved CR at the 3-month Visit (3 months after the first instillation of UGN-103) as determined by cystoscopy, for cause biopsy, and urine cytology. If response cannot be evaluated for a patient at the 3-month Visit (due to death, lost to follow-up, or indeterminate results), the patient will be considered an NCR for the purpose of analysis and will be included in the denominator.

The two-sided 95% exact CI for the CRR will be derived by a test for binomial proportions (SAS PROC FREQ with binomial option) using the Clopper-Pearson method (Clopper and Pearson, 1934). Reasons for NCR will be tabulated using the number and percentage of patients.

Subgroup Analysis

The following subgroups will be explored to determine any prominent trend in the primary efficacy data provided subgroups have a sufficient number of patients in each category to result in meaningful analyses.

Subgroups will include (but are not limited to):

- Age group (< 65, ≥ 65 years)
- Body mass index category (< 30 kg/m^2, ≥ 30 kg/m^2)
- Sex (male, female)
- Treatment course (full course 6 treatments, partial course < 6 treatments)
- Tumor size (> 3 cm, ≤ 3 cm)
- Tumor (single, multiple)
- Recurrence within 1 year of current diagnosis (0 vs ≥ 1)
- Prior TURBT (≤ 2, > 2)

The frequency and percentage of CR (primary endpoint) along with the 95% exact CI will be presented for each of the above covariates (subgroups) using the safety analysis set.

The summary will also be displayed by a forest plot.

9.4.3 Secondary Efficacy Endpoints

Duration of Response

DOR in patients who achieved CR at the 3-month Visit is defined as the time from the date of evidence of CR at the 3-month Visit to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, or death due to any cause, whichever occurred first.

The distribution of DOR will be estimated using the Kaplan-Meier method. Median DOR, first and third quartiles, and 95% CIs (Brookmeyer and Crowley, 1982) will be estimated. A figure and listing of DOR will also be provided.

Handling of Missing Values/Censoring/Discontinuations

If a patient has not had an event (recurrence or progression or death), DOR will be censored at the date of the last adequate disease assessment (ie, a visit when all scheduled disease assessments have been done). Details of the censoring rules will be provided in the statistical analysis plan (SAP).

Durable Complete Response Rate at Scheduled Disease Assessment Time Points

DCR rate at scheduled disease assessment time points in patients who achieved CR at the 3-month Visit is defined as the proportion of patients who maintained CR (ie, no detectable disease) up to that particular follow-up disease assessment. DCR rate will be presented with 95% exact CI (Clopper-Pearson) at each scheduled time point.

9.4.4 Exploratory Efficacy Endpoint

Preliminary responses following SoC treatment in 3-month NCR patients will be summarized descriptively.

9.4.5 Safety Analysis

Safety analyses will be conducted using the safety analysis set. The assessment of safety will be mainly based on the incidence of AEs and the number of laboratory values that fall outside of pre-determined ranges. Other safety data (eg, physical examination, vital signs) will be considered as appropriate.

Adverse Events and Serious Adverse Events

Summary tables for AEs will include only AEs that started or worsened during the study (TEAEs). However, all safety data including those collected during the pre-treatment period will be listed and flagged.

The incidence of TEAEs (new or worsening from baseline) will be summarized by system organ class and/or preferred term (PT), severity (based on CTCAE grades), type of AE, and relation to study treatment.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE.

AESIs will be considered. A comprehensive list of reported AE terms based on clinical review will be used to identify Medical Dictionary for Regulatory Activities (MedDRA) PTs for each of the AESI categories. The list of terms to be used for each category of AESI may be based on the safety review team (SRT) agreements in place at the time of reporting. The SRT agreements are based on a review of the MedDRA dictionary.

Summaries of the number and percentage of patients with these events will be provided for each type of event. Further details will be provided in the SAP.

Clinical Laboratory Data

Analyses of safety laboratory data will be performed for all collected laboratory parameters. Laboratory data will be graded according to CTCAE version 5.0 (CTCAE, 2017), if applicable.

In some cases (eg, white blood cell differentials), the lower limits of normal ranges used in CTCAE definition may need to be replaced by a clinically meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Data will be summarized and listed separately for hematology, biochemistry, and urinary laboratory tests as appropriate and will be specified in the SAP.

Physical Examination

General physical examination will be performed at Screening only. Urological examination will be performed at Screening and during treatment visits. Details are provided in Section 1.3 and Section 8.2.1. Any clinically relevant changes of urological examination will be recorded on the AE sections of the eCRF and reported with AEs as described above.

Vital Signs

The following analysis will be performed for vital signs:

- Shift table baseline to worst on-treatment result
- Table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points

Definitions of clinically notable abnormal results will be specified in the SAP. Patients exhibiting clinically notable vital sign abnormalities will be listed.

9.4.6 Pharmacokinetic Analysis

Descriptive statistics for concentrations of UGN-103 and calculated PK parameters will be performed on the PK analysis set and will include the number of participants, mean, standard deviation, median, minimum, maximum, and coefficient of variation. Geometric means will be computed for PK parameters only, and only mean/median, minimum, and maximum will be reported for t_{max}.

9.4.7 Patient-Reported Outcome Measures

An exploratory objective of the study is to assess the effect of treatment with UGN-103 on PRO measures. The PRO assessment plan includes the EORTC QLQ-C30 (Appendix 2) and the TSQM (Appendix 3). Analyses will be based on the safety analysis set.

Descriptive statistics will be used to summarize the scored scales for each of the questionnaires at each scheduled assessment time point. Additionally, change from baseline in the domain scores at the time of each assessment will be summarized. Patients with an evaluable baseline score and at least one evaluable post baseline score will be included in the change from baseline analyses.

Scoring of raw quality of life data and methods to deal with missing items or missing assessments will be handled according to the standard scoring guidelines for each patient questionnaire. The number of patients completing each patient questionnaire and the number of missing or incomplete assessments will be summarized for each scheduled assessment time point for the QLQ-C30 and TSQM questionnaires. Full details of the analysis of PRO measures will be provided in the SAP.

9.4.8 Biomarker Analysis

No formal hypotheses will be tested. Findings from correlative analysis will be reported separately and will not be included in the clinical study report (CSR).

9.4.9 Other Analysis

Additional analyses may be performed and will be described in the SAP.

9.5 Interim Analysis

No formal interim analysis is planned for this study.

The final analysis will be performed after all patients have completed the study, withdrawn consent, been lost to follow-up, died during the study, or when the study is closed by the sponsor.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations (including EU CTR 536/2014)

For sites outside the EU, the protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. For sites in the EU, the study sponsor or its delegate will perform submissions to the member states for study review as defined by the EU CTR 536/2014.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Protocols and any substantial amendments to the protocol will require health authority approval before initiation except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Finance and Insurance

10.1.3.1 Finance

The study is financed by the sponsor as detailed in the financial agreement between the sponsor and the investigator/institution.

10.1.3.2 Insurance

The study will be covered in accordance with local requirements and per the clinical trial agreement. An insurance certificate will be supplied to the contract research organization/ investigator as necessary.

10.1.4 Informed Consent Process

10.1.4.1 Consent and Other Informational Documents Provided to Patients

Consent forms describing in detail the study treatment, study procedures, and risks are given to the patient, and written documentation of informed consent is required before initiating any study procedures and starting study treatment. The ICF is submitted with this protocol.

The statement of informed consent must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, EU CTR 536/2014, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

10.1.4.2 Consent Procedures and Documentation

Informed consent is a process that is initiated before the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB approved, and the patient will be asked to read and review the document. The investigator or his/her representative will explain the nature of the study to the patient or their legally authorized representative and answer all questions regarding the study. A verbal explanation will be provided in terms suited to the patient's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research patients. Patients will have the opportunity to carefully review the written consent form and ask questions before signing. The patients should have the opportunity to discuss the study with their family or surrogates or think about it before agreeing to participate.

Patients must be informed that their participation is voluntary and that they may withdraw from the study at any time, without prejudice, regardless of the patient's relationship with the study center, investigator, or sponsor, if applicable. Patients or their legally authorized representative defined as per the applicable country-specific regulations will be required to sign a statement of informed consent before any procedures being done specifically for the study.

The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the patient undergoes any study-specific procedures. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or their legally authorized representative.

Patients who are re-screened are required to sign a new ICF.

10.1.5 Data Protection, Confidentiality, and Privacy

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor should contain the identifier only; patient names or any information that would make the patient identifiable should not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required, depending on the requirements of local law, to either acknowledge or agree that their data may be used as described in the informed consent.

The patient must be informed that his/her medical/pharmacy records and records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. The investigative site will permit access to such records.

Patient confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests (if applicable) in addition to the clinical information relating to patients. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure

location for as long a period as dictated by the reviewing IRB, institutional policies, local regulations, or sponsor requirements.

Appropriate technical and organizational measures are in place to ensure the appropriate security of personal data, including protection against unauthorized or unlawful processing and against accidental loss, destruction, or damage.

In the event of a personal data breach, the sponsor will perform a risk assessment. In compliance with applicable regulations (US, EU, or local), if a personal data breach notification is required, investigators will be alerted to contact the affected patient(s); the sponsor/sponsor's designee will also notify the proper regulatory authorities.

10.1.6 Data Review Committee

Not applicable.

The decision to not form an independent data monitoring committee is justified by the lack of associated cancer-specific mortality and the low risk of disease progression in the target patient population, and the overall favorable safety profile of mitomycin for intravesical solution.

10.1.7 Dissemination of Clinical Study Data

Data collected for this study will be analyzed and stored by the sponsor. After the study is completed, the de-identified, archived data will be transmitted to and stored by the sponsor, for use by other researchers including those outside of the study. Permission to transmit data to the sponsor will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through the sponsor.

10.1.8 Safety Oversight

Safety oversight will be under the direction of the sponsor. Safety will be assessed throughout the course of the study by the sponsor SRT.

10.1.9 Clinical Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary, depending on recruitment frequency at each site. The monitor will record dates of the visits in an investigative site visit log that will be kept at the site. Monitoring of patient Screening data will be performed on all patients to ensure eligibility. The first post-initiation visit will be made as soon as possible (approximately 2-3 weeks) after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and investigational staff and are

accessible for verification by the sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation (medical records) must be allowed for verifying that the data recorded in the eCRF is consistent with the original source data. Findings from this review of eCRFs and source documents will be discussed with the investigational staff. The sponsor expects that, during monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct. Further details of clinical site monitoring including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) will be provided in a study monitoring plan (SMP). The SMP will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

Independent audits may be conducted by representatives of the sponsor's clinical quality assurance department or their designee to ensure that monitoring practices are performed consistently across all participating sites and that monitors are following the SMP.

10.1.10 Data Quality Assurance

All patient data relating to the study will be recorded on eCRF. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

Guidance on completion of eCRFs will be provided in the eCRF Completion Guidelines.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Quality tolerance limits (QTLs) or quality control (QC) checks identify systematic issues that can impact patient safety and/or reliability of study results. These QTLs or QC checks (ie, data QC checks) will be implemented for the EDC. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Following written Standard Operating Procedures, the monitors will verify that the clinical study is conducted, data are generated, and biological specimens are collected, documented (ie, recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, Good Laboratory Practices).

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).

Study patient research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the sponsor. This will not include the patient's contact or identifying information. Rather, individual patients and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the sponsor's research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the sponsor.

10.1.11 Data Handling and Record Keeping

10.1.11.1 Data Collection and Management Responsibilities

This study will use an EDC system; the designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs are built using fully validated, secure, web-enabled software that conforms to 21 CFR Part 11 requirements. Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs and allow modification or verification of the entered data by the investigator staff.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. It is the sponsor's expectation that data required by the protocol will be entered by the clinical site staff in a timely manner according to guidance provided.

Clinical data will be entered directly from the source documents. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data and if applicable, signed or initialed and dated.

Hard copies of the study visit worksheets may be provided for use as source document worksheets for recording data for each patient enrolled in the study. Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Study Records Retention

Study documents should be retained for a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed during the retention period without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. No records may be transferred to another location or party without written notification to the sponsor.

10.1.12 Protocol Deviations

A protocol deviation is a departure from the study protocol and/or study related documents. The departure may be either on the part of the site or the patient and identified as site or patient deviations. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

Protocol deviations related to study inclusion or exclusion criteria, conduct of the study, patient management or patient assessment should be addressed in study source documents and reported to the sponsor. Protocol deviations must be submitted to the local or central IRB/IEC according to their guidelines. The site PI/study staff are responsible for knowing and adhering to their IRB/IEC requirements.

In the event of a serious breach of the regulations or the protocol version applicable at the time of the breach, the sponsor will notify regulatory authorities according to region or country-specific requirements. A "serious breach" is a breach likely to affect to a significant degree the safety and rights of a patient or the reliability and robustness of the data generated in the study.

10.1.13 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.14 Study and Site Start and Closure

Study Start Date

The study start date is the date of first site activation.

Study/Site Termination

The sponsor or designee reserves the right to close the investigative site or terminate the study at any time for any reason at the sole discretion of the sponsor. Investigative sites will be closed upon study completion. An investigative site is considered closed when all required documents and study supplies have been collected and an investigative site closure visit has been performed.

The investigator may initiate investigative site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigative site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development
- Determination of unexpected, significant, or unacceptable risk to patients
- Demonstration of efficacy that would warrant stopping
- Determination that the primary endpoint has been met

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of patients by the investigator
- Total number of patients included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate patient therapy and/or follow-up.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB, and/or relevant health authorities.

10.1.15 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

The sponsor will provide a CSR (or its summary) within one year of the study completion date to the regulatory agencies and IECs, as applicable, according to country-specific requirements.

For EU countries, the sponsor will submit final results of the clinical study to the Clinical Trials Information System (CTIS) database (https://euclinicaltrials.eu/home) in a timely manner irrespective of the study outcome. As appropriate, the final study results posting will be accompanied by a summary written in a manner that is understandable to laypersons.

10.1.16 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. The sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

11 REFERENCES

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Appendix 1. Guidance on Evaluation of Response

Response will be evaluated based on visual observation by cystoscopy (white light), histopathology of any remaining/new lesions (by central pathology lab), and urine cytology (by central pathology lab) at the 3-month Visit and every 3 months thereafter during the Follow-up Period.

Complete response (CR): A patient will be considered to have a CR if there is no detectable disease (NDD) in the bladder by cystoscopy, biopsy (if indicated), and urine cytology.

Non-complete response (NCR): There is evidence of the disease under study at the 3-month Visit.

Recurrence: There is evidence of the disease under study at a follow-up visit. Note: The criteria to define NCR and Recurrence are the same.

Indeterminate: The criteria for determining either CR or NCR/Recurrence is not fulfilled due to incomplete or missed assessment. Questionable interpretations must be resolved and not be assessed as indeterminate. In case the evaluation of response is "indeterminate" at the 3-month Visit or a follow-up visit, sites must perform the required procedures as soon as possible to have an adequate response evaluation.

All required procedures must be performed at efficacy assessment visits to determine the overall response of a patient. However, for clarity the response evaluation has been broken down by each procedure (1 & 2). Both are combined in Table 9 to determine the overall response of a patient.

1. Evaluation Based on Cystoscopy and Biopsy/Histopathology

a. If any lesion(s) appear endoscopically, even if they appear necrotic, the physician must biopsy the visible lesion(s). If the histopathology reveals malignancy, the patient's response will be recorded as NCR/Recurrence.

b. If visual assessment indicates no remaining lesions or histopathology reveals no malignancy of the remaining lesions, then it is determined as NDD.

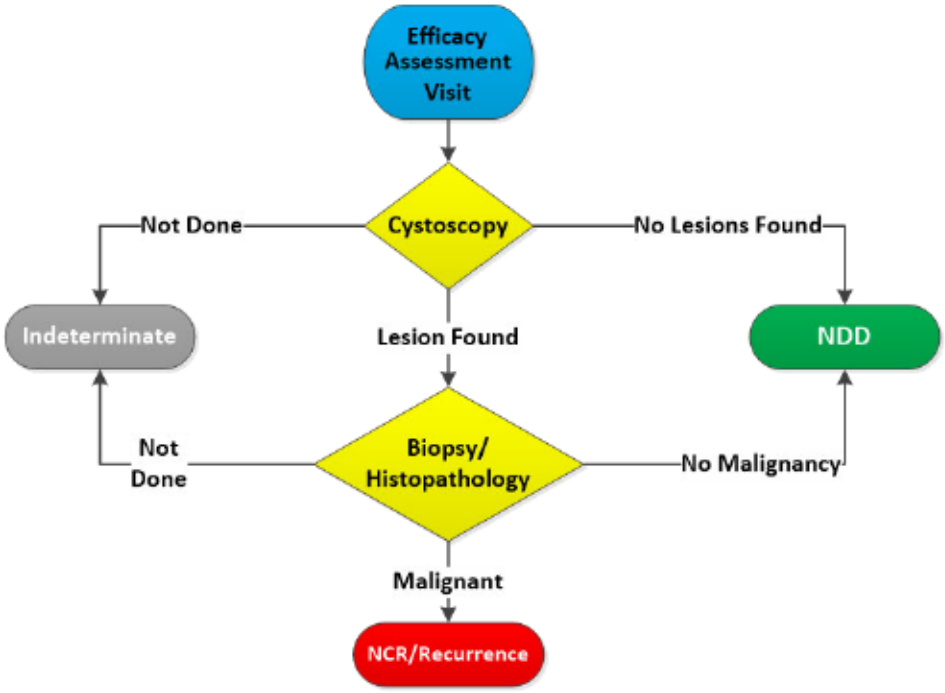
c. If cystoscopy was not performed and/or the biopsy was not done when indicated, the evaluation will be indeterminate.

Table 7 Evaluation Based on Cystoscopy and Biopsy/Histopathology

Lesion Found by Cystoscopy?	Biopsy Done?	Histopathology Result	Evaluation
Yes	Yes	Malignant	NCR/Recurrence
Yes	Yes	No malignancy	NDD
No	NA	-	NDD
Yes	No	-	Indeterminate
Not done	-	-	Indeterminate

NA = not applicable; NCR = non-complete response; NDD = no detectable disease.

Figure 2 Evaluation Based on Cystoscopy and Biopsy/Histopathology



2. Evaluation Based on Urine Cytology, Diagnosis of UTUC, and Random Bladder Biopsies (If indicated)

Urine Cytology Results

Urine cytology specimens will be analyzed using Paris classification and can have the following main outcomes which will be collected in the eCRF:

1. Atypical cells
2. Negative for high grade urothelial carcinoma (HG UC)
3. Other malignancies, primary and metastatic
4. HG UC
5. Low grade urothelial carcinoma (LG UC)
6. Suspicious for HG UC
7. Unsatisfactory specimen

Note: A central laboratory urine cytology report with a result of "Negative for high grade urothelial carcinoma including low grade urothelial neoplasm" should be interpreted and documented as option 2 (Negative for high grade urothelial carcinoma) in the eCRF.

Evaluation of Response

a. If the results are interpreted as 1, 2, or 3 above, then NDD is determined by cytology.

b. If the cytology result indicates either HG UC (4) or LG UC (5) or is suspicious for HG UC (6) then the results should be correlated with the cystoscopy or biopsy findings.

   i. If there are no visible lesions on cystoscopy, or a biopsy reveals no evidence of LG NMIBC, the urine cytology must be repeated.

   ii. If the repeat cytology result is either 1, 2, or 3, then NDD is determined by cytology.

   iii. If the repeat cytology result remains 4, 5, or 6, the investigator must exclude upper tract urothelial carcinoma (UTUC) and occult carcinoma of the bladder or urethra.

      (1) If UTUC is diagnosed, then NDD is determined by cytology.

      (2) If UTUC is not diagnosed, then the investigator must perform random bladder biopsies (RBB). Biopsies will be carried out to examine the following 6 bladder mucosal sites: bladder floor, right wall, left wall, dome, posterior wall, and prostatic urethra (in males) or bladder neck (in females).

         (a) If the histopathology of any of these biopsies reveals malignancy, the patient's response will be recorded as NCR/Recurrence.

         (b) If the histopathology reveals no malignancy, then it is determined as NDD.

c. If either cytology, and/or required repeat cytology, and/or upper tract evaluation (as indicated), and/or RBB of the bladder (as indicated) is not performed, the evaluation will be indeterminate.

d. If the cytology result is inconclusive due to unsatisfactory specimen, the sample must be retaken as soon as possible. The response will be determined following criteria a) through c). Evaluations based on an unsatisfactory specimen will be indeterminate.

Table 8 Evaluation Based on Urine Cytology, Diagnosis of UTUC, and Random Bladder Biopsies

Cytology Results	Repeat Cytology Required? [a]	Repeat Cytology Results	Evaluation to Exclude UTUC?	UTUC Diagnosed?	Evaluation
1) Atypical cells or 2) Negative for HG UC or 3) Other malignancies, primary and metastatic	NA	-	NA	-	NDD
4) HG UC or 5) LG UC or 6) Suspicious for HG UC	Yes	1 or 2 or 3	NA	-	NDD
4 or 5 or 6	Yes	4 or 5 or 6	Yes	Yes	NDD
4 or 5 or 6	Yes	4 or 5 or 6	Yes	Not done	Indeterminate
4 or 5 or 6	Yes	Not done	-	-	Indeterminate
4 or 5 or 6	Yes	4 or 5 or 6	Yes	No [b]	Will be determined by the results of the biopsies [c]
Not done	-	-	-	-	Indeterminate

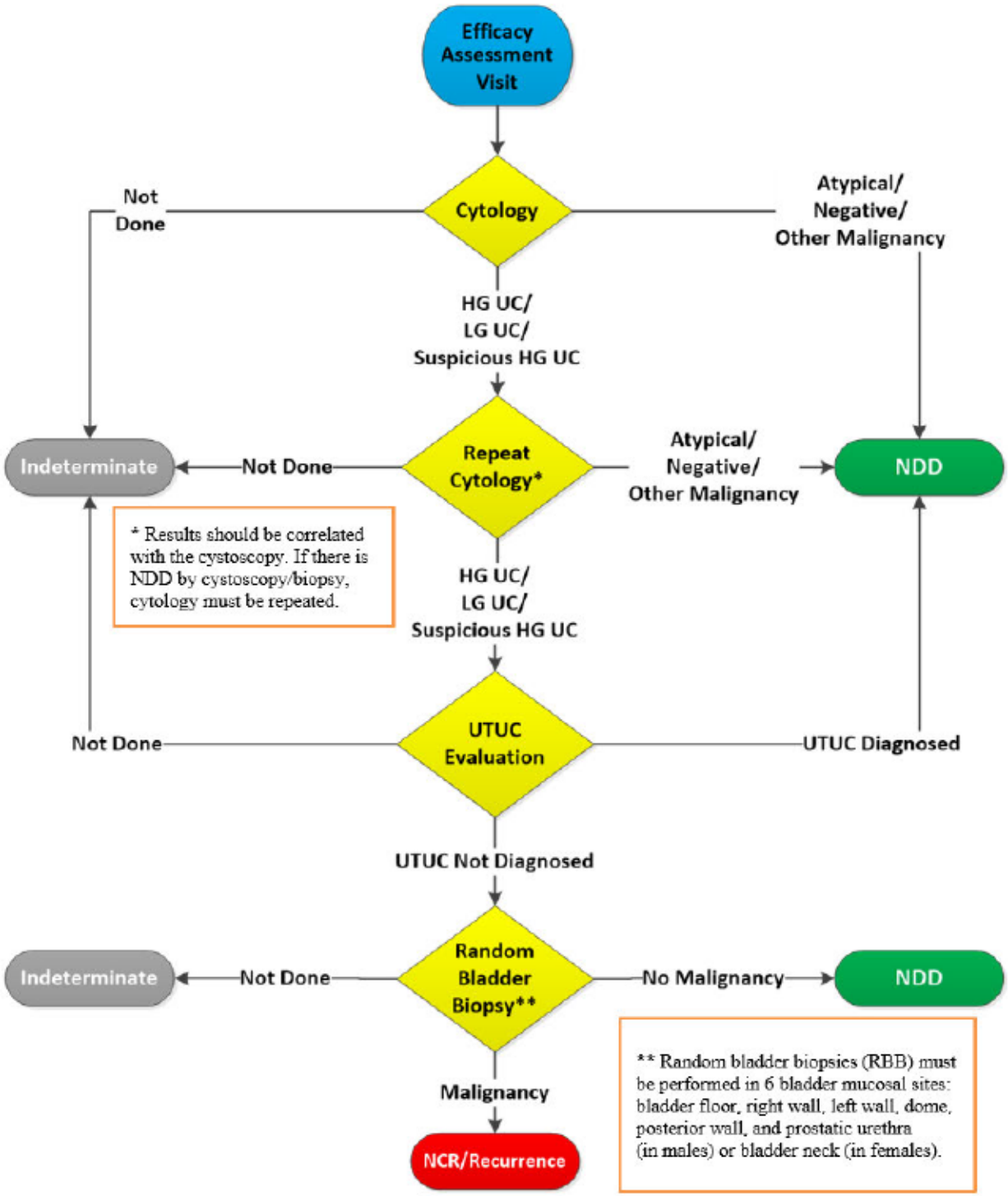
HG = high grade; LG = low grade; NA = not applicable; NCR = non-complete response; NDD = no detectable disease; UC = urothelial carcinoma; UTUC = upper tract urothelial carcinoma.

[a] Results should be correlated with the cystoscopy. If there is NDD by cystoscopy/biopsy, cytology must be repeated.

[b] Random bladder biopsies (RBB) must be performed in 6 bladder mucosal sites: bladder floor, right wall, left wall, dome, posterior wall, and prostatic urethra (in males) or bladder neck (in females).

[c] If the result indicates no malignancy, then NDD will be determined, otherwise, if the result indicates malignancy, then evaluation of response will be recorded as NCR/Recurrence.

Figure 3 Evaluation Based on Urine Cytology, Diagnosis of UTUC, and Random Bladder Biopsies



3. Overall Response Based on Cystoscopy, Biopsy/Histopathology, Cytology, Diagnosis of UTUC, and Random Bladder Biopsies

a. If there is evidence of UC by either of the methods (cystoscopy followed by biopsy/ histopathology or urine cytology), the patient will be recorded as NCR (3-month Visit) or Recurrence (follow-up visit), irrespective of the outcome of the other procedure, even if it was not done.

b. Else if evaluation is indeterminate by either or both methods the evaluation of response is indeterminate.

c. Otherwise, the evaluation of response is CR.

Table 9 Evaluation of Response Based on All Assessments

Cystoscopy/Histopathology	Cytology/UTUC Diagnosis/ Random Bladder Biopsies	Evaluation of Response (To Be Entered in the CRF)
NDD	NDD	CR
NDD	NCR/Recurrence	NCR/Recurrence
NDD	Indeterminate [a]	Indeterminate
NCR/Recurrence	NDD	NCR/Recurrence
NCR/Recurrence	NCR/Recurrence	NCR/Recurrence
NCR/Recurrence	Indeterminate	NCR/Recurrence
Indeterminate	NDD	Indeterminate
Indeterminate	NCR/Recurrence	NCR/Recurrence
Indeterminate	Indeterminate	Indeterminate

CR = complete response; CRF = case report form; NCR = non-complete response; NDD = no detectable disease; UTUC = upper tract urothelial carcinoma.

[a] These scenarios will be adjudicated on a case-by-case basis.

[redacted]



[redacted]

[redacted]

[redacted]

[redacted]

Appendix 4. Protocol Revision History

Version	Date	Description of Changes	Brief Rationale
4.0	06 Aug 2025	• Updated key roles and contact information	Personnel changes
		• Revised on-site follow-up visit windows to occur not earlier than and within 2 weeks after the scheduled month in Section 1.3	[redacted]
		• Clarified the timing of follow-up visits is relative to the 3-month Visit and not the start of study treatment	[redacted]
		• Noted in Appendix 1 how to document central laboratory urine cytology results reported using the 2nd edition of The Paris System	[redacted]
		• Other minor revisions and formatting changes have been made throughout the document	Clarify intent and ensure internal consistency
3.0	11 Apr 2024	• Added short-term follow-up of 3-month NCR patients in Sections 1.1, 1.2, 1.3, 3, 4.1, 7, 9.3, and 9.4.4	[redacted]
		• Increased the size of the PK subgroup from 6 patients to 9-12 patients	[redacted]
		• Increased the number of investigative sites from approximately 45 to 55	Ensure enough sites are included to complete enrollment in the expected timeframe
		• Revised the list of AESIs in Section 8.3.9	[redacted]
		• Other minor revisions and formatting changes have been made throughout the document	Clarify intent and ensure internal consistency
2.0	21 Feb 2024	• Added the study name/acronym to the protocol title and document header	More clearly identify the study to investigative sites
		• Updated key roles and contact information	Personnel changes
		• Edited the study rationale/background in Sections 1.1, 2.1, and 2.2	Alignment with interdependent IND (application) documents
		• Added an exploratory analysis of PRO measures (QLQ-C30 and TSQM) in Sections 1.1, 1.3, 3, 8.4, 9.4.6, Appendix 2, and Appendix 3	To assess the effect of UGN-103 on disease related symptoms and treatment satisfaction

Version	Date	Description of Changes	Brief Rationale
		• Added an exploratory analysis of tumor tissue from archival biopsies and/or on study visits in Sections 1.1, 1.3, 3, 8.1.5, 8.8, and 9.4.7	To identify mechanisms of sensitivity and/or resistance to UGN-103
		• Revised inclusion criterion 4 from a history of at least 1 prior episode of LG NMIBC to NMIBC	The study aims to enroll patients with recurrent NMIBC, and from a clinical perspective, the prior episode(s) could be low or high grade
		• Increased the number of investigative sites from approximately 40 to 45	Ensure enough sites are included to complete enrollment in the expected timeframe
		• Other minor revisions and formatting changes have been made throughout the document	Clarify intent and ensure internal consistency