TITLE PAGE

Protocol Title: A Phase 3, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of UGN-102 as Primary Chemoablative Therapy in Patients with Low Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence

Protocol Number: BL011

Compound: UGN-102 (mitomycin) for intravesical solution

Study Phase: 3

Short Title: A Phase 3 Single-Arm Study of UGN-102 for Treatment of LG IR NMIBC

Sponsor Name: UroGen Pharma Ltd.

Legal Registered Address:
9 Ha'Ta'asiya Street
Ra'anana, Israel 4365405
[redacted]

Regulatory Agency Identifier Number(s):
IND: 138749
EU CT Number: 2023-506680-34

Protocol Status	Version	Date
Original	1.0	12 Nov 2021
Amendment 1	2.0	21 Dec 2021
Amendment 2	3.0	20 Apr 2022
Amendment 3	4.0	04 May 2022
Amendment 4	5.0	28 Feb 2024

KEY ROLES AND CONTACT INFORMATION

Sponsor Medical Monitor
[redacted], MBBS, UroGen Pharma
[redacted]

Study Director
[redacted], UroGen Pharma
[redacted]

Medical Monitor, Europe
[redacted], MD, [redacted]
[redacted]

Study Logistics
[redacted], UroGen Pharma
[redacted]

Quality Assurance
[redacted], UroGen Pharma
[redacted]
qa@urogen.com

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

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 consent form 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 consent form 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 consent form.

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of UGN-102 as Primary Chemoablative Therapy in Patients with Low Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence

Short Title: A Phase 3 Single-Arm Study of UGN-102 for Treatment of LG IR NMIBC

Rationale: Patients with LG NMIBC are currently treated with transurethral resection of bladder tumors (TURBT), usually under general anesthesia. There is no approved medicinal product for primary treatment. A subset of patients with LG NMIBC (intermediate risk population) experiences repeated recurrence of tumors requiring repetitive surgical intervention, which is associated with significant postoperative and long-term morbidity and an increased risk of mortality. Therefore, UroGen is developing UGN-102 as a first-line nonsurgical alternative to TURBT.

This Phase 3 study is designed to confirm the results of a Phase 2b, single-arm, multicenter study in 63 patients with LG IR NMIBC (BL005), which demonstrated that intravesical instillation of UGN-102 once-weekly for 6 weeks results in high rates of complete response (CR) at 3 months and durable complete response (DCR) at 12 months after the start of study treatment. Forty-one (65.1%) patients achieved the primary endpoint of CR at 3 months after the first instillation of UGN-102 (95% confidence interval [CI] of CR rate: 52.0, 76.7), and 25/41 (61.0%) patients had a DCR at 12 months after the first instillation (95% CI of DCR rate: 44.5, 75.8). The 9-month duration of response (DOR) rate as estimated by the Kaplan Meier method was 72.5% (95% CI: 54.4, 84.3), ie, the probability that a patient will maintain CR for at least 9 months is 72.5%.

Overall, 57/63 (90.5%) patients had at least 1 treatment-emergent adverse event (TEAE), and 40/63 (63.5%) patients had at least 1 study drug or procedure related TEAE. There were low rates of TEAEs leading to treatment discontinuation (6/63 [9.5%] patients) and serious TEAEs (5/63 [7.9%] patients), and no serious TEAEs were related to study drug or procedure. Renal and urinary disorders were the most commonly reported TEAEs (44/63 [69.8%] patients). TEAEs were primarily mild to moderate in severity (50/57 [87.7%] patients), and there were no clinically meaningful trends or pattern of changes in laboratory parameters, vital signs, or physical examinations.

Objectives and Endpoints

Objective	Endpoint
Primary	
• To evaluate the tumor ablative effect 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-102) as determined by cystoscopy, for cause biopsy, and urine cytology

Key Secondary	
• To evaluate the durability of response with respect to DOR	• 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
Other Secondary	
• To evaluate the durability of response with respect to DCR rate at scheduled disease assessment time points and DFS	• 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 • DFS in patients who achieved CR at the 3-month Visit, defined as the time from first dose 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
• To evaluate the safety and tolerability of intravesical instillations of UGN-102 in patients with LG NMIBC	• The safety profile of UGN-102 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)
Exploratory	
• To evaluate TTR following SOC treatment in patients who have NCR at the 3-month Visit	• TTR in patients who were NCR (residual disease) at the 3-month Visit, defined as the time from the date of first treatment after NCR to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, whichever occurred first
• To evaluate the preliminary responses following SOC treatment in 3-month CR patients who have disease recurrence or progression during the Follow-up Period	• Number (%) of response outcomes evaluated at the first disease assessment visit after SOC
• To evaluate the impact of UGN-102 on subsequent SOC treatment in patients who have NCR at the 3-month Visit or disease recurrence or progression during the Follow-up Period	• Proportion of patients whose planned NMIBC treatment at baseline was downgraded following treatment with UGN-102 (eg, from TURBT to biopsy and/or fulguration)
• To assess the effect of UGN-102 on PRO measures including disease related symptoms and physical, mental, and social health	• Changes from baseline in patient scores on the QLQ-C30 and QLQ-NMIBC24 questionnaires

AE = adverse event; AESI = adverse event of special interest; CR = complete response; CRR = complete response rate; DCR = durable complete response; DFS = disease-free survival; DOR = duration of response; LG = low grade; NCR = non-complete response; NMIBC = non-muscle-invasive bladder cancer; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire for Cancer Patients; QLQ-NMIBC24 = 24-item Quality of Life Questionnaire for NMIBC; SAE = serious adverse event; SOC = standard of care; TTR = time to recurrence; TURBT = transurethral resection of bladder tumors.

Overall Design

This Phase 3, multinational, single-arm, multicenter study will evaluate the efficacy and safety of UGN-102 as primary chemoablative therapy in patients with LG IR 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 receive 6 once-weekly intravesical instillations of UGN-102. The UGN-102 concentration to be used in this study will be 1.33 mg mitomycin per 1 mL admixture. The volume of UGN-102 admixture to be instilled will be 56 mL (75 mg mitomycin).

All patients will return to the clinic approximately 3 months after the first instillation for determination of response to treatment. Assessment of response will be 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 confirmed to have a 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. Patients confirmed to have a non-complete response (NCR) will undergo Investigator designated standard of care (SOC) treatment of remaining lesions and then enter the Follow-up Period of the study.

During the Follow-up Period, patients will return to the clinic every 3 months for up to 24 months (ie, 27 months after the first instillation) for evaluation of response. Patients who remain disease free at the 27-month Visit will continue to return to the clinic every 6 months for up to 36 months (ie, 63 months after the first instillation) or until disease recurrence, disease progression, death, or the study is closed by the Sponsor, whichever occurs first.

Patients confirmed to have a disease recurrence during the Follow-up Period or a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment 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-102 and qualified per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 as Grade 3 or 4.

Number of Patients: Approximately 220 patients will be enrolled.

Inclusion Criteria

1. Capable of giving 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 signing the ICF.

3. Patient who has LG NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening.

4. History of LG NMIBC requiring treatment with TURBT. 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).

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)/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 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 mitomycin 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 grading 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 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.

Intervention Groups and Duration: Patients will receive 6 once-weekly intravesical instillations of UGN-102 (75 mg mitomycin). The total duration of study participation for each participant is up to 63 months (from first instillation to last visit).

Statistical Considerations

Statistical Hypothesis: No formal hypotheses will be tested for the confirmation of efficacy. Hypotheses are only provided for the justification of the sample size of this study. Confirmation of efficacy will be determined by the clinical meaningfulness of the primary and key secondary endpoints.

Sample Size: Approximately 220 patients will be enrolled in this study to justify the efficacy outcomes of the study based on the primary (complete response rate [CRR] at 3 months) and key secondary (DOR) endpoints.

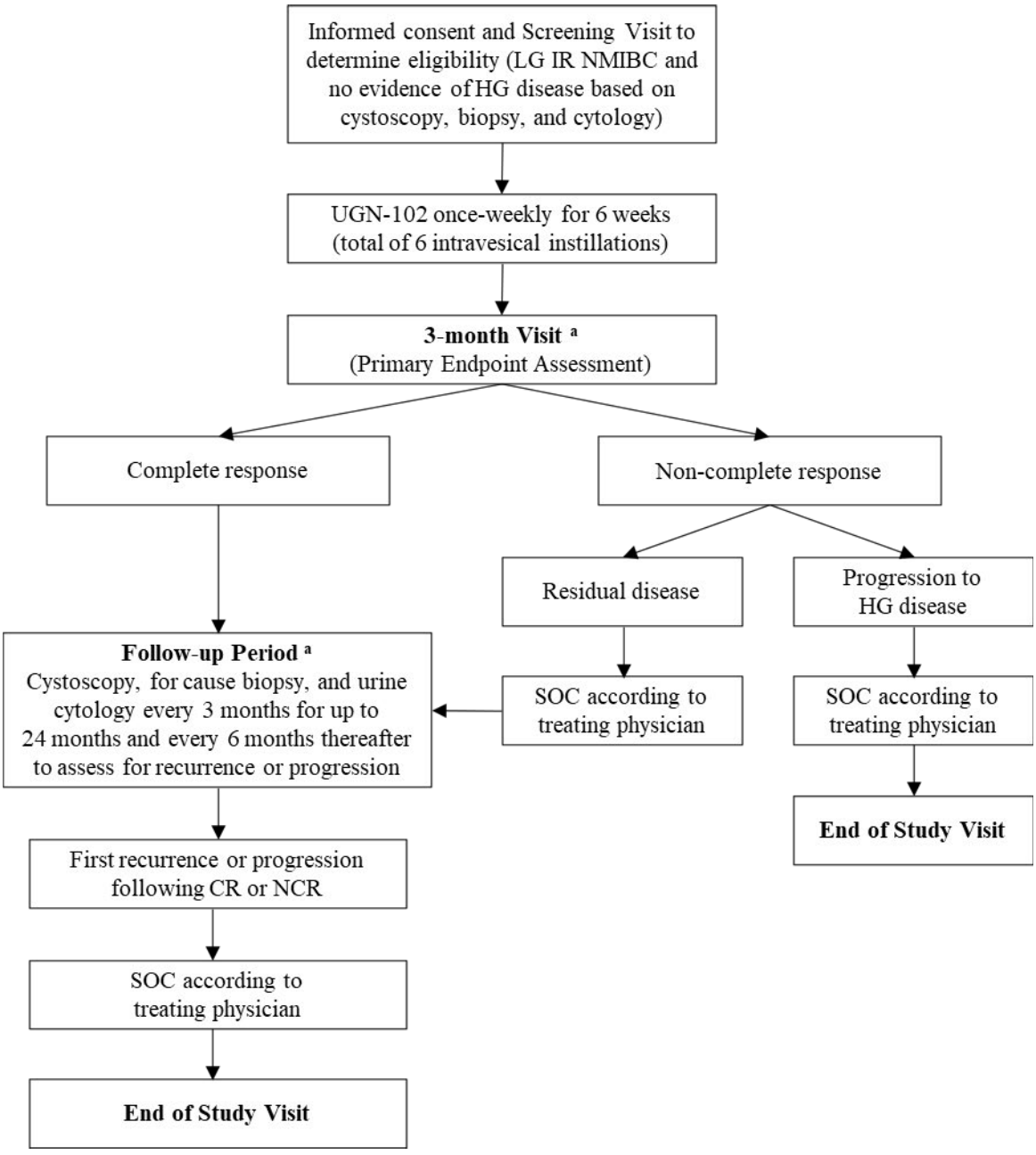
Statistical Analyses: Point estimates of the primary endpoint CRR at 3-month Visit and secondary endpoint DCR at scheduled disease assessment time points along with their exact 95% CIs will be summarized. The time to event endpoints (DOR and disease-free survival [DFS]) will be estimated using the Kaplan-Meier method.

No formal interim analysis is planned for this study.

The actual time point of the primary analysis will be determined based on the emerging data.

The EOS analysis will be performed after all patients complete the study, are withdrawn from the study, are lost to follow-up, or when the study is closed by the Sponsor. Primary results of all relevant endpoints will be updated using the final data.

1.2 Schema



CR = complete response; EOS = end of study; HG = high grade; IR = intermediate risk; LG = low grade; NCR = non-complete response; NMIBC = non-muscle-invasive bladder cancer; SOC = standard of care.

[a] Patients confirmed to have a disease recurrence during the Follow-up Period or a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate EOS Visit performed.

1.3 Schedule of Activities

Procedures	**Screening Period** [a]	**Treatment Period**							**3-M DAV** [b, c]	**Follow-up Period** [c] **(Visits start at M6 and continue until recurrence, progression, or death is documented)**					**EOS** [d]	
															CR	**R or P**
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**	**q 3 months until M27**	**q 6 months after M27**	**M63**	**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**	**±2 w**	**±2 w**	**±2 w**	**±1 w**
Informed consent	X [f]															
Inclusion/exclusion criteria	X															
Demographics	X															
Medical/surgical and smoking history	X [g]															
Concomitant medication review	X [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
General physical examination [i]	X															
Urological examination [j]	X	X	X	X	X	X	X									
Height and weight	X															
Vital signs [k]	X	X	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 [l]	X	X	X	X	X	X	X		X			X	X	X	X	
Pregnancy test (WOCBP only) [m]	X	X							X							
Administer QLQ-C30 and QLQ-NMIBC24 [n]	X	X	X	X	X	X	X		X			X	X	X	X	
Qualitative interviews (patients at participating US sites) [o]	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 [p]	X															
Cystoscopy (white light) [q]	X								X			X	X	X	X	
Cold cup biopsy (send to central lab) [q]	X															
Urine cytology (send to central lab)	X [r]								X			X	X	X	X	
Biopsy remaining lesions if indicated by cystoscopy (send to central lab)									X			X	X	X	X	
Administer study treatment		X	X	X	X	X	X									
Complete eCRFs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess outcome of treatment of recurrence or progression [s]																X

AE = adverse event; ASA = American Society of Anesthesiologists; 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; MRI = magnetic resonance imaging; NA = not applicable; NCR = non-complete response; NMIBC = non-muscle-invasive bladder cancer; P = progression; q = every; QLQ-C30 = Quality of Life Questionnaire for Cancer Patients; QLQ-NMIBC24 = 24-item Quality of Life Questionnaire for NMIBC; R = recurrence; SOC = standard of care; TC = telephone contact; TURBT = transurethral resection of bladder tumors; UC = urothelial carcinoma; US = United States; 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 confirmed to have a CR at the 3-month Visit will enter the Follow-up Period of the study. Patients confirmed to have a NCR will undergo Investigator designated SOC treatment of remaining lesions and then enter the Follow-up Period of the study. Details of the SOC provided (eg, treatment modality, use and type of anesthesia, outcome, associated AEs) will be documented.
c. Patients confirmed to have a disease recurrence during the Follow-up Period or a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate EOS Visit performed. Details of the SOC provided (eg, treatment modality, use and type of anesthesia, outcome, associated AEs) will be documented.
d. Patients who remain disease free at the 57-month Visit will have procedures specified for the 63-month Visit as their EOS assessments. The timing of the EOS Visit for patients who have a disease recurrence or progression during the Follow-up Period will be 3 months (±1 week) after SOC treatment of disease recurrence or progression.
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. Including ASA Physical Status classification (ASA, 2020) based on the Investigator's assessment.
h. Any past therapy (eg, pharmacological or surgical interventions) related to UC will be recorded during Screening. In addition, the patient's attitude about surgery (eg, willing, unwilling) and the default planned LG NMIBC treatment had the patient not been enrolled in the trial will be collected at baseline for all enrolled patients.
i. 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.
j. The urological examination should be performed before cystoscopy at the Screening Visit. 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.
k. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.
l. Dipstick on-site (all visits); central laboratory urinalysis with culture and sensitivity when clinically indicated by abnormal local laboratory results.
m. Urine or serum pregnancy test (at local laboratory).
n. The QLQ-C30 and QLQ-NMIBC24 should be administered before cystoscopy or before administration of study treatment at relevant visits. During the Follow-up Period, the QLQ-C30 and QLQ-NMIBC24 will be administered only to patients who achieved CR at the 3-month Visit.
o. Exploratory qualitative interviews will be performed to better understand the experience of participants during the trial and how participants compared treatment with UGN-102 to a previous TURBT procedure.
p. 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).
q. 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. This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of the tumor is not to be performed. If, in the Investigator's assessment, tumors present on cystoscopy are sufficiently heterogenous in presentation such that one biopsy is not adequate, more than one biopsy sample can be taken.
r. No cytology needed if results from a prior cytology within 8 weeks before Screening are available.
s. Assessments should be performed as appropriate to the needs of the visit.

ABBREVIATIONS

3-month$_{CR}$	CR at 3-month disease assessment (analysis set)
3-month$_{NCR}$	NCR at 3-month disease assessment (analysis set)
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ASA	American Society of Anesthesiologists
AST	Aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
CFR	Code of Federal Regulations
CI	Confidence interval
CIS	Carcinoma in situ
CR	Complete response
CRR	Complete response rate
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAV	Disease assessment visit
DCR	Durable complete response
DFS	Disease-free survival
DOR	Duration of response
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
FDA	Food and Drug Administration
FUP$_{NCR}$	NCR at follow-up disease assessment (analysis set)
GCP	Good clinical practice
GGT	Gamma glutamyltransferase
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
IR	Intermediate risk

IRB	Institutional review board
ITT	Intent-to-treat (analysis set)
LG	Low grade
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NA	Not applicable
NCR	Non-complete response
NDD	No detectable disease
NMIBC	Non-muscle-invasive bladder cancer
P	Progression
PI	Principal Investigator
PP	Per protocol (analysis set)
PQC	Product quality complaint
PRO	Patient-reported outcome
PT	Preferred term
QC	Quality control
QLQ-C30	Quality of Life Questionnaire for Cancer Patients
QLQ-NMIBC24	24-item Quality of Life Questionnaire for NMIBC
QTL	Quality tolerance limit
R	Recurrence
RBB	Random bladder biopsies
SAE	Serious adverse event
SAP	Statistical analysis plan
SEER	Surveillance, Epidemiology, and End Results (Program)
SMP	Study monitoring plan
SoA	Schedule of activities
SOC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TC	Telephone contact
TEAE	Treatment-emergent adverse event
TTR	Time to recurrence
TURBT	Transurethral resection of bladder tumors
UC	Urothelial carcinoma
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeia
UTI	Urinary tract infection
UTUC	Upper tract urothelial carcinoma
WOCBP	Women of childbearing potential

2 INTRODUCTION

Non-Muscle-Invasive Bladder Cancer

Bladder cancer is the sixth most common cancer in the US, with approximately 84,000 new cases diagnosed in 2021 (ACS, 2021). At the time of diagnosis, 75% of patients present with NMIBC (Babjuk et al, 2019; Monteiro et al, 2019). NMIBC includes a clinically heterogeneous group of cancers with a wide range of recurrence and progression probabilities (Chang et al, 2016). Therefore, treatment guidelines recommend classifying patients with NMIBC as being at low, intermediate, or high risk of disease recurrence and/or progression (Babjuk et al, 2019; Chang et al, 2016; Kamat et al, 2014). While the management of low risk and high-risk patients appears clear, the best treatment option for intermediate risk patients remains undefined (Monteiro et al, 2019). Based on analysis of the Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database, UroGen estimates that LG IR NMIBC represents approximately 25% of newly diagnosed bladder cancer cases in the US (SEER Program, 2019).

The current SOC for treatment of LG IR NMIBC is TURBT, usually under general anesthesia (NCCN, 2021; Chang et al, 2016). Due to the persistent and recurrent nature of the disease (30% to 50% recur at 1 year; Babjuk et al, 2019), patients with LG IR NMIBC often endure repeated TURBTs under general anesthesia, which research has shown to be associated with significant postoperative and long-term morbidity and an increased risk of mortality (Erikson et al, 2020; Pereira et al, 2019; Avallone et al, 2017; Ghali et al, 2016; Matulewicz et al, 2015; Patel et al, 2015; De Nunzio et al, 2014; Hollenbeck et al, 2006; Balbay et al, 2005). Rates of 30-day complications (11%), unplanned hospital readmissions (5%), and mortality (1%) following TURBT yield a significant number of patients at risk given the high volume of this procedure (Erikson et al, 2020; Patel et al, 2015; Rambachan et al, 2014). The totality of evidence, including procedural limitations (eg, incomplete resection of tumors; Daneshmand et al, 2018; Miyake et al, 2016), postoperative complications, and the high recurrence rate of NMIBC, suggests that the current, primarily surgical approach to treatment is suboptimal.

Short-term, chemoablative therapy with UGN-102 has the potential to serve as a primary nonsurgical treatment option for LG IR NMIBC, especially among this population of predominantly elderly and multimorbid patients, by whom surgery and anesthesia are poorly tolerated. Studies in the peer-reviewed literature (Lindgren et al, 2020; Mostafid et al, 2020; Colombo et al, 2012) and data from the UGN-102 clinical development program suggest that chemoablation with mitomycin may obviate the need for surgery in some patients or reduce the perioperative morbidity associated with surgery secondary to lower volume disease, and may be associated with fewer clinically significant adverse effects.

UGN-102

UGN-102 (mitomycin) for intravesical solution is a reverse thermal gel formulation of mitomycin designed for initial nonsurgical treatment of LG IR NMIBC, and to potentially obviate the need for repetitive TURBT. The reverse thermal properties of UGN-102 allow for the local administration of mitomycin as a liquid in a cooled state, with subsequent conversion to a semi-solid gel depot at body temperature following instillation into the bladder cavity. The gel

slowly disintegrates and is excreted by normal urine flow, allowing for the sustained release of mitomycin over a period of 4 to 6 hours. The prolonged exposure of tumor cells to mitomycin leads to improved chemoablation compared with aqueous preparations of mitomycin.

The efficacy and safety of UGN-102 for the treatment of patients with LG IR NMIBC was evaluated in a Phase 2b, single-arm, multicenter study (BL005). Intravesical instillation of UGN-102 once weekly for 6 weeks resulted in high rates of CR at 3 months and DCR at 12 months after the start of study treatment. A total of 63 patients were enrolled and treated with UGN-102. Forty-one (65.1%) patients achieved the primary endpoint of CR at 3 months after the first instillation of UGN-102 (95% CI of CR rate: 52.0, 76.7), and 25/41 (61.0%) patients had a DCR at 12 months after the first instillation (95% CI of DCR rate: 44.5, 75.8). The 9-month DOR rate as estimated by the Kaplan-Meier method was 72.5% (95% CI: 54.4, 84.3), ie, the probability that a patient will maintain CR for at least 9 months is 72.5%.

Overall, 57/63 (90.5%) patients had at least 1 TEAE, and 40/63 (63.5%) patients had at least 1 study drug or procedure related TEAE. There were low rates of TEAEs leading to treatment discontinuation (6/63 [9.5%] patients) and serious TEAEs (5/63 [7.9%] patients), and no serious TEAEs were related to study drug or procedure. Renal and urinary disorders were the most commonly reported TEAEs (44/63 [69.8%] patients). TEAEs were primarily mild to moderate in severity (50/57 [87.7%] patients), and there were no clinically meaningful trends or pattern of changes in laboratory parameters, vital signs, or physical examinations.

Further details regarding the development of UGN-102 can be found in the UGN-102 Investigator's Brochure (IB).

2.1 Study Rationale

Patients with LG NMIBC are currently treated with TURBT, usually under general anesthesia. There is no approved medicinal product for primary treatment. A subset of patients with LG NMIBC (intermediate risk population) experiences repeated recurrence of tumors requiring repetitive surgical intervention, which is associated with significant postoperative and long-term morbidity and an increased risk of mortality. Therefore, UroGen is developing UGN-102 as a first-line nonsurgical alternative to TURBT.

Development of UGN-102 as an alternative to TURBT is informed by physician and patient perspectives on the current SOC and dissatisfaction with the lack of alternatives to repetitive TURBT for the treatment of patients with recurrent NMIBC.

An April 2021 web-based survey of 100 urologists in the US found that 46% of physicians are dissatisfied with current treatment alternatives for recurrent LG NMIBC, and 36% of physicians believe their patients are also dissatisfied (data on file at UroGen). Half or more of physicians surveyed expressed concern about the risk of general anesthesia required for TURBT (51%), the risk of perforation with TURBT procedures (63%), and 55% believed that repeated TURBT procedures are not appropriate for all LG NMIBC patients. Physicians estimate that approximately 20% of their LG NMIBC patients are not good candidates for TURBT due to

being frail/elderly, not a candidate for anesthesia, having cardiovascular disease or renal disease, or based on characteristics of the bladder and/or tumor.

In addition, a web-based survey of 350 NMIBC patients in the US and Canada who had undergone 1 or more TURBTs assessed treatment preference between two hypothetical options, surgical therapy (TURBT) versus intravesical chemoablation without surgery, and reasons for treatment preference. A substantial proportion of patients surveyed (40%) preferred chemoablation over TURBT. Predictors of treatment preference for chemoablation included US residence (p=0.02), more recent TURBT experience (p=0.03), high tumor grade (p=0.03), or expressed priority of recurrence risk (p<0.0001) (Parisse et al, 2021).

This Phase 3 study is designed to confirm the results of a Phase 2b, single-arm, multicenter study in 63 patients with LG IR NMIBC (BL005), which demonstrated that intravesical instillation of UGN-102 once-weekly for 6 weeks results in high rates of CR at 3 months and DCR at 12 months after the start of study treatment (Section 2).

2.2 Benefit-Risk Assessment

Further details regarding the benefit-risk profile of UGN-102 for treatment of LG IR NMIBC can be found in the UGN-102 IB.

2.2.1 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 UGN-102. 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 30 to 60 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.

2.2.2 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 UGN-102 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.

2.2.3 Overall Benefit-Risk Conclusion

Overall, based on the efficacy and safety results observed to date, UGN-102 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-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-102) as determined by cystoscopy, for cause biopsy, and urine cytology
Key Secondary	
• To evaluate the durability of response with respect to DOR	• 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
Other Secondary	
• To evaluate the durability of response with respect to DCR rate at scheduled disease assessment time points and DFS	• 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 • DFS in patients who achieved CR at the 3-month Visit, defined as the time from first dose 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
• To evaluate the safety and tolerability of intravesical instillations of UGN-102 in patients with LG NMIBC	• The safety profile of UGN-102 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)
Exploratory	
• To evaluate TTR following SOC treatment in patients who have NCR at the 3-month Visit	• TTR in patients who were NCR (residual disease) at the 3-month Visit, defined as the time from the date of first treatment after NCR to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, whichever occurred first
• To evaluate the preliminary responses following SOC treatment in 3-month CR patients who have disease recurrence or progression during the Follow-up Period	• Number (%) of response outcomes evaluated at the first disease assessment visit after SOC
• To evaluate the impact of UGN-102 on subsequent SOC treatment in patients who have NCR at the 3-month Visit or disease recurrence or progression during the Follow-up Period	• Proportion of patients whose planned NMIBC treatment at baseline was downgraded following treatment with UGN-102 (eg, from TURBT to biopsy and/or fulguration)
• To assess the effect of UGN-102 on PRO measures including disease related symptoms and physical, mental, and social health	• Changes from baseline in patient scores on the QLQ-C30 and QLQ-NMIBC24 questionnaires

AE = adverse event; AESI = adverse event of special interest; CR = complete response; CRR = complete response rate; DCR = durable complete response; DFS = disease-free survival; DOR = duration of response; LG = low grade; NCR = non-complete response; NMIBC = non-muscle-invasive bladder cancer; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire for Cancer Patients; QLQ-NMIBC24 = 24-item Quality of Life Questionnaire for NMIBC; SAE = serious adverse event; SOC = standard of care; TTR = time to recurrence; TURBT = transurethral resection of bladder tumors.

4 STUDY DESIGN

4.1 Overall Design

This Phase 3, multinational, single-arm, multicenter study will evaluate the efficacy and safety of UGN-102 as primary chemoablative therapy in patients with LG IR 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 receive 6 once-weekly intravesical instillations of UGN-102. The UGN-102 concentration to be used in this study will be 1.33 mg mitomycin per 1 mL admixture. The volume of UGN-102 admixture to be instilled will be 56 mL (75 mg mitomycin).

All patients will return to the clinic approximately 3 months after the first instillation for determination of response to treatment. Assessment of response will be 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 (Section 8.1.2). Any lesions or suspect tissue must be biopsied to evaluate for persistence of disease.

Patients confirmed to have a 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. Patients confirmed to have a NCR will undergo Investigator designated SOC treatment of remaining lesions and then enter the Follow-up Period of the study. Details of the SOC provided (eg, treatment modality, use and type of anesthesia, outcome, associated AEs) will be documented.

During the Follow-up Period, patients will return to the clinic every 3 months for up to 24 months (ie, 27 months after the first instillation) for evaluation of response. Patients who remain disease free at the 27-month Visit will continue to return to the clinic every 6 months for up to 36 months (ie, 63 months after the first instillation) or until disease recurrence, disease progression, death, or the study is closed by the Sponsor, whichever occurs first.

Patients confirmed to have a disease recurrence during the Follow-up Period or a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate EOS Visit performed. Details of the SOC provided (eg, treatment modality, use and type of anesthesia, outcome, associated AEs) will be documented. The timing of the EOS Visit will be 3 months (±1 week) after SOC treatment of disease recurrence or progression.

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-102 (Section 8.3.1.3.3) and qualified per National Cancer Institute CTCAE version 5.0 as Grade 3 or 4 (Section 8.3.1.3.1).

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

Study Population

Patients in this study will have a history of at least 1 prior episode of LG NMIBC requiring treatment with TURBT. The histological diagnosis of LG NMIBC (Ta) will be confirmed by thorough cystoscopy and cold cup biopsy of visualized tumor at Screening or within 8 weeks before Screening according to international guidelines on the management of NMIBC (Babjuk et al, 2019; Monteiro et al, 2019; Chang et al, 2016). Negative voiding cytology for HG disease is required within 8 weeks before Screening. The definition of IR disease in this study is multiple or recurrent LG Ta tumors, or solitary LG Ta tumor > 3 cm, as proposed by the International Bladder Cancer Group (Kamat et al, 2014).

Most Ta LG tumors will experience disease recurrence, but very few of them will experience disease progression to a higher grade or stage (Marcq et al, 2019). Therefore, other key eligibility criteria were selected to ensure that patients have evidence of the disease under study, with a tumor burden sufficient to demonstrate treatment effect, but not exceeding what is reasonably expected to be eradicated by treatment with UGN-102. Patients with a history of muscle invasive or metastatic disease, and patients with a recent history of high risk NMIBC (eg, HG, CIS) or who have received treatments that would suggest a history of aggressive bladder tumors are purposefully excluded.

Clinical practice guidelines do not recommend mapping biopsies of normal appearing urothelium for the target patient population, particularly in the absence of a positive cytology, because random biopsies rarely yield positive results (NCCN, 2021; Babjuk et al, 2019; Monteiro et al, 2019; Chang et al, 2016). Therefore, the study protocol mandates biopsies of any lesions or suspect tissue to evaluate for persistence of disease. Biopsies for assessment of efficacy are not indicated in the absence of visible disease because this would subject patients to more invasive procedures than prescribed by current clinical practice guidelines.

Primary and Secondary Endpoints

CR (ie, tumor eradication) and DOR (ie, durability of effect) are considered compelling measures of clinical benefit and directly attributable to drug effect given the absence of nonsurgical therapies for primary treatment of LG NMIBC, and that LG NMIBC lesions do not spontaneously remit without treatment (Hurle et al, 2018). Durable CR has supported traditional approval in multiple cancers when there was no approved drug therapy.

CRR at the 3-month Visit is the primary endpoint of this study and the same primary endpoint as in Phase 2b Study BL005. CR is prospectively defined and based on standard urologic practices, including direct visualization of the bladder (white light cystoscopy), histopathology of any remaining/new lesions (by central pathology lab), and urine cytology (by central pathology lab). Thus, there are objective assessments used in determining response.

DOR is a secondary endpoint and will be measured by following patients who achieve a CR at the 3-month Visit. DOR is defined as the time from the date of evidence of CR at the 3-month Visit to the earliest date of disease recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, or death due to any cause, whichever occurred first.

Single-Arm Design

This Phase 3 study is designed to confirm the results of Phase 2b Study BL005, which demonstrated a robust treatment response and encouraging durability data for UGN-102 in the treatment of LG IR NMIBC (Section 2). The current study is similar in design to Study BL005 but has a larger sample size and a longer Follow-up Period, and also will include follow-up of NCR patients and prospective data collection for SOC treatments administered after UGN-102 in NCR patients and patients with disease recurrence or progression.

Given the lack of an approved medicinal product to serve as active comparator and based on the understanding that bladder tumors do not spontaneously remit, a properly powered single-arm study is considered appropriate to demonstrate substantial evidence of efficacy and safety attributable to UGN-102 for the treatment of LG IR NMIBC.

4.3 Dose Justification

The UGN-102 dose (75 mg mitomycin) was chosen based on efficacy and tolerability. Study BL003 demonstrated a numerically higher CRR for the 75 mg dose compared to the 37.5 mg dose. In Study BL004, the 120 mg dose had a similar response rate and a higher rate of AEs than the 75 mg dose in Study BL003. Study BL005 showed a favorable efficacy and safety profile with 6 once-weekly instillations of 75 mg. Results showed high rates of CR at 3 months and DCR at 12 months after the start of study treatment. The overall safety profile of UGN-102 comprised primarily mild to moderate AEs, no treatment-related serious adverse events (SAEs) or hospitalizations, low rate of AEs leading to treatment discontinuation, and no clinically meaningful trends or pattern of changes in laboratory parameters, vital signs, or physical examinations.

4.4 End of Study Definition

The EOS is defined as the last patient last visit.

EOS will be declared after all patients have completed the EOS Visit, died during the study, withdrawn consent, been lost to follow-up, or when the study is closed by the Sponsor.

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

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. Capable of giving 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 signing the ICF.

3. Patient who has LG NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening.

4. History of LG NMIBC requiring treatment with TURBT. 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).

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/ALT ≤ 2.5 × ULN.
   - ALP ≤ 2.5 × ULN.
   - 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).

5.2 Exclusion Criteria

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

1. Received BCG treatment for UC within previous 1 year.
2. History of HG bladder cancer (papillary or CIS) in the past 2 years.
3. Known allergy or sensitivity to mitomycin 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 grading 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.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical 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 220 patients with LG IR NMIBC are enrolled in the study. Patients who discontinue before the EOS Visit may be replaced at the Sponsor's discretion. The study will be conducted at approximately 80 to 90 investigative sites in the US and Europe that provide care to patients with bladder cancer.

5.6 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 outside the pre-defined parameters, treatment may be postponed for up to 4 weeks until the clinical event resolves and/or laboratory values improve (Section 8.2.3.1).

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

The UGN-102 admixture for intravesical instillations contains mitomycin 75 mg in 56 mL admixture (1.33 mg mitomycin per 1 mL). The UGN-102 admixture is prepared in advance of use by the qualified location for drug preparation (typically, the pharmacy), and it is stable for up to 48 hours before administration at room temperature (this time is supported by in-use stability data for up to 48 hours) plus 1 additional hour in ice to facilitate instillation. The UGN-102 single dose carton contains the below listed components (Table 1).

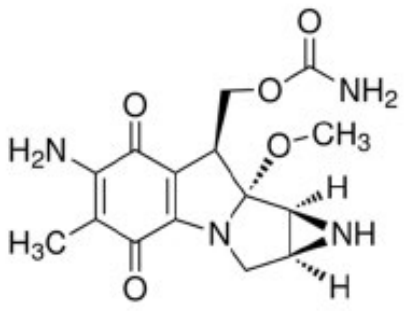
Table 1 UGN-102 Components

Component	Quantity (per single dose carton) [a]	Function
Mitomycin for Solution (vial)	2 × 40 mg	Active Ingredient
Sterile Hydrogel (vial)	1 × 60 mL	Vehicle
UGN-102 Admixture Labels	3	Admixture labels
Instructions for Pharmacy	1	Instructions for admixture
Instructions for Administration	1	Instructions for instillation

[a] For the proposed indication, each 40 mg vial of mitomycin will be mixed with 3 mL sterile water for injection and 27 mL sterile hydrogel. A total of 56 mL of the 1.33 mg/mL admixture will be instilled in each patient. The hydrogel and mitomycin excess included are to allow for the required UGN-102 volume withdrawal from the vials.

Refer to 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 40 mg mitomycin for solution are manufactured for UroGen Pharma Ltd., 9 Ha'Ta'asiya Street, Ra'anana, Israel, by [redacted]. Mitomycin is provided as a dry lyophilized powder in 100 mL vials and will be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F and 86°F) and not to exceed 40°C (104°F).

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

Table 2 Vial Composition of Mitomycin for Solution

Component	Quantity (mg per vial)	Pharmaceutical Grade	Function
Mitomycin	40 mg	USP	Active ingredient
Mannitol	80 mg	USP	Bulking agent

USP = United States Pharmacopeia.

The 60 mL of sterile hydrogel in a 100-ml glass vial are manufactured for UroGen Pharma Ltd., 9 Ha'Ta'asiya Street, Ra'anana, Israel, by [redacted]. Sterile hydrogel is provided in a 100-mL glass vial and will be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F and 86°F) and not to exceed 40°C (104°F) (Refer to Label for Hydrogel Vial).

The contents of each sterile hydrogel vial are a proprietary mixture of poloxamer 407, hydroxypropyl methyl cellulose, polyethylene glycol, and water for injection.

The components of UGN-102 are produced under aseptic conditions and according to current Good Manufacturing Practice (GMP) (European Commission, May 2003 Guidelines). The UGN-102 lots to be used in this study are tested and released under supervision and approval by the Sponsor or Sponsor's Designee.

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-102 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-102 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.
- Conduct training for pharmacy personnel on UGN-102 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 30 to 60 minutes after each study treatment instillation.

Mitomycin concentration	UGN-102 volume	Route of administration [a]
1.33 mg/mL	56 mL	Local administration into the bladder

[a] Refer to UGN-102 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-102 instillations are expected to occur at the study site on an ambulatory basis.

6.2 UGN-102 Single Dose Carton/Handling/Storage/Accountability

6.2.1 Acquisition and Accountability

UGN-102 single-dose carton is assembled for UroGen Pharma Ltd. 9 Ha'Ta'asiya St., Ra'anana, Israel 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.

The Sponsor's Designee will ship all drugs to the pharmacy/approved designee at a controlled temperature between 15°C and 30°C (59°F and 86°F). The shipping temperature will be monitored and recorded by temperature-monitoring device loggers.

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-102 must be available for verification by the Sponsor's site monitor during on-site monitoring visits. Unused or expired UGN-102 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-102 single dose cartons will be marked "not for use" in pen over the label and stored separately from usable UGN-102 single dose cartons.

Replacement UGN-102 will be supplied after 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-102 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-102 is 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

UGN-102 single dose carton must be stored at a controlled temperature of 20°C to 25°C (68°F to 77°F), excursion permitted between 15°C and 30°C (59°F and 86°F). Exposure to excessive heat (over 40°C, 104°F) should be avoided.

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

The UGN-102 admixture (sterile hydrogel mixed with mitomycin) is stable for 48 hours at 20°C to 25°C (68°F to 77°F), excursion permitted between 15°C and 30°C (59°F and 86°F). Exposure to excessive heat (over 40°C, 104°F) should be avoided. Up to 1 hour before administration, the admixture should be cooled down to between -3°C (27°F) and +5°C (41°F) in order to liquify the UGN-102. 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, or during transport to patient's home, the Investigator is responsible for notifying the Sponsor about the defect/temperature deviation. Any PQCs must be reported to the Sponsor/Sponsor Designee using: [redacted] or [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/Sponsor 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 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

In addition, the patient's attitude about surgery (eg, willing, unwilling) and the default planned LG NMIBC treatment had the patient not been enrolled in the trial will be collected at baseline for all enrolled patients.

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
- TURBT

Note: Prohibited medications and procedures apply to all patients until either NCR at the 3-month Visit (NCR patients) or disease recurrence or progression during the Follow-up Period (CR patients). At such times, patients are to be treated with Investigator designated SOC, which may include therapies from the list of prohibited concomitant medications and procedures.

Details of the SOC provided (eg, treatment modality, use and type of anesthesia, outcome, associated AEs) will be documented.

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 Sponsor Medical Monitor should be contacted 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.

6.8 Treatment of Overdose

Not applicable.

7 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

A patient who has completed the EOS Visit, died during the study, or who is still in follow-up when EOS is declared will be considered to have completed the study.

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 (including, but not limited to, changes from baseline) after enrollment, 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 defined by the parameters below, treatment may be postponed for up to 4 weeks until the clinical event resolves and/or laboratory values improve (Section 8.2.3.1):

- Absolute neutrophil count ≤ 1,000/µL (≤ 1.0×10^9/L).
- Platelets ≤ 80,000/µL (≤ 80×10^9/L).
- AST and/or ALT ≥ 5 × ULN.
- Laboratory evidence of active UTI.

If the clinical event does not resolve and/or the laboratory values do not improve after 4 weeks, the Investigator should contact the UroGen Medical Monitor.

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
- Study is closed or terminated by the Sponsor

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

At the time of discontinuation from the study, an EOS Visit (Month 63) should be conducted as shown in the Schedule of Activities (SoA). See Section 1.3 for data to be collected at the time of study discontinuation and for any further evaluations that need to be completed. The patient will be permanently discontinued both from the study treatment and from 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.

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 CRF. 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.

8.1 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 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 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. For more details, refer to Appendix 1 (Guidance on Evaluation of Response).

- **CR:** A patient will be considered to have had 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 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 having 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 had 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, then the patient is considered NCR. Note: Biopsy results showing papillary urothelial neoplasm of low malignant potential (PUNLMP) are not considered cancer and in such cases the patient would be considered CR.

- **Recurrence:** All patients will be assessed for recurrence every 3 months for up to 24 months after the 3-month Visit (ie, 27 months after the first instillation). Patients who remain disease free at the 27-month Visit will continue to be assessed for recurrence every 6 months for up to 36 months (ie, 63 months after the first instillation) or until disease recurrence, disease progression, death, or the study is closed by the Sponsor, 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 8.1.4 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 that atypical cells identified on urine cytology are not consistent with LG NMIBC or malignancy in general, and that 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 UC of the upper tract and occult carcinoma of the bladder or urethra.
  - If UTUC is confirmed, the patient will be considered as 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 having 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, sites must perform the required procedures as soon as possible in order to have an adequate response evaluation.

8.1.3 Classification of Partial Response

Partial response is defined as a sufficient reduction in tumor burden such that the planned NMIBC treatment before study enrollment is downgraded at the discretion of the Investigator to a less invasive option following treatment with UGN-102 (eg, from TURBT to biopsy and/or fulguration).

8.1.4 Assessment of Tumor Progression

The overall risk of progression for patients with LG papillary NMIBC at intermediate risk of recurrence ranges from approximately 1 to 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.

Patients confirmed to have a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate EOS Visit performed. The timing of the EOS Visit will be 3 months (±1 week) after SOC treatment of disease progression.

8.1.5 Assessment of Tumor Recurrence

Follow-up will be conducted in patients who were defined as having CR or NCR (after undergoing Investigator designated SOC treatment of remaining lesions) at the 3-month Visit.

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 defined as having recurrence, complete documentation should be obtained.

Patients confirmed to have a disease recurrence during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate EOS Visit performed. The timing of the EOS Visit will be 3 months (±1 week) after SOC treatment of the recurrence.

8.1.6 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. No samples will be used for non-study related purposes.

8.2 Safety Assessments

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

- Evaluation (frequency, seriousness, severity, and type) of AEs including adverse events 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 Cardiovascular system Respiratory system HEENT (head, eyes, ears, nose, and throat) and neck Abdomen Extremities Neurologic system Skin	Urethral meatus Perineal skin and mucus membranes Scrotum and testes (for male patients) Lymphadenopathy

[a] Performed before cystoscopy at relevant 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 Laboratory Safety Assessments

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

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EDC = electronic data capture; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyltransferase.
Note: Laboratory samples will be kept per storage requirements as stated in the laboratory manual until shipped to the central laboratory for analysis.

The Investigator must review the laboratory report, 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 clinically indicated by abnormal local laboratory results.

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 ≤ 1,000/µL (≤ 1.0×10^9/L).
- Platelets ≤ 80,000/µL (≤ 80×10^9/L).
- AST and/or ALT ≥ 5 × ULN.
- Laboratory evidence of active UTI.

If the clinical event does not resolve and/or the laboratory values do not improve after 4 weeks, the Investigator should contact the UroGen Medical Monitor.

8.2.3.2 Urinalysis

Samples will be collected for urinalysis, including culture and sensitivity (if suggestive of infection) at the Screening Visit 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 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.

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

The definitions of AEs and SAEs can be found in Section 8.3.1. All 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 as per instructions in Section 8.3.2 and remain responsible for following up all applicable AEs including those that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment or from 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 the 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 until 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 Visit 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 TEAEs.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. 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 conclusion of the 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 (as defined in 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 Designee about the above by completing and submitting the ***SAE/Death or Pregnancy eCRF*** 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 along with 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 the Food and Drug Administration (FDA) 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 FDA and all participating Investigators in an Investigational New Drug 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 or Pregnancy eCRF***.

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.

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 off-line 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 6 months after the last dose of UGN-102. 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 partner, 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 determination of AESIs and Investigators are to report all AEs in a consistent manner as described in Section 8.3.2.

As the predominant AESIs are Renal and urinary disorders and relate to local effects of UGN-102 administration, 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.

The list of AESIs is based on the most current safety profile of UGN-102 within the overall clinical development program and through ongoing review of emerging safety data.

Current known AESIs include:

- Allergic reaction to mitomycin (CTCAE Grade 3 or 4)
- Voiding interruption due to urethral/penile edema (unrelated to prostatic hypertrophy)
- Indication of bone marrow suppression
- Lower urinary tract symptoms (CTCAE Grade 3 or 4)

8.4 Patient-Reported Outcome Measures

The patient-reported outcome (PRO) assessment plan for this study was guided by an empirically derived conceptual framework of anticipated side effects following treatment for NMIBC that are important from the perspectives of patients and their managing clinicians (Rutherford et al, 2017).

The European Organisation for Research and Treatment of Cancer (EORTC) questionnaires for cancer patients (QLQ-C30) (Section 8.4.1) and patients with NMIBC (QLQ-NMIBC24) (Section 8.4.2) are intended to be administered together and collectively assess all of the potential side effects in the Rutherford et al (2017) conceptual framework, including side effects during treatment (eg, pain when urinating) and long-term symptoms (eg, sexual functioning). Both scales are available in more than 40 languages. Additional data on the patient's perception of treatment with UGN-102 will be collected through qualitative interviews with a subset of patients at Screening and after the 3-month Visit (Section 8.4.3).

Planned time points for all PRO measures are provided in the SoA (Section 1.3). The QLQ-C30 and QLQ-NMIBC24 should be administered before cystoscopy or before administration of study treatment at relevant visits.

8.4.1 Side Effect Questionnaire for Cancer Patients (QLQ-C30)

The EORTC 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 time frame for the items is the past week.

The EORTC QLQ-C30 is designed for use with a wide range of cancer patient populations and is intended to be supplemented by tumor-specific questionnaire modules (Section 8.4.2). Reference values for specific cancer populations are available, including bladder cancer (Jung et al, 2020; Yu et al, 2019; Scott et al, 2008). In addition, European and North American general population norm data are available to facilitate valid intra- and inter-country comparisons and score interpretation (Nolte et al, 2019).

The QLQ-C30 is provided in Appendix 2.

8.4.2 Side Effect Questionnaire for Patients With NMIBC (QLQ-NMIBC24)

The EORTC QLQ-NMIBC24 is a 24-item measure that assesses side effects specific to NMIBC and its treatments, including urinary symptoms, sexual function, bloating and flatulence, malaise, future health worries, and intravesical treatment issues. The time frame for the items is the past week, except for sexual function, which is the past 4 weeks.

The QLQ-NMIBC24 is provided in Appendix 3.

8.4.3 Qualitative Interviews

Exploratory qualitative interviews will be performed with patients at participating US sites to better understand the experience of participants during the trial and how participants compare their treatment with UGN-102 to a previous TURBT procedure in terms of impact on daily activities, recovery time, and which they would recommend to other NMIBC patients. Details of this exploratory analysis will be described in a separate report.

8.5 Pharmacokinetics and Pharmacodynamics

Pharmacokinetic and pharmacodynamic parameters are not evaluated in this study.

8.6 Genetics

Genetics are not evaluated in this study.

8.7 Biomarkers

Biomarkers are not evaluated in this study.

8.8 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 hypotheses will be tested for the confirmation of efficacy. The hypotheses described in Section 9.2 are only for the justification of the sample size of this study. Confirmation of efficacy will be determined by the clinical meaningfulness of the primary and key secondary endpoints.

9.2 Sample Size Determination

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

The key secondary endpoint DOR will be used to assess the long-term treatment effect in patients who responded at the 3-month Visit. 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 rule will be provided in the Statistical Analysis Plan (SAP).

The median DOR was not achieved in Study BL005. There are limited published data for DOR following TURBT in LG NMIBC. Based on the results published in the European Association of Urology Guidelines on NMIBC (TaT1 and CIS) - 2019 Update (Babjuk et al, 2019), the 1 year DFS rate of TURBT is 50% (ie, median DFS of 12 months). The clinical hypothesis is that the treatment effect of UGN-102 will be similar to TURBT.

In order to ensure 80% power to test the null hypothesis: 1 year DOR rate = 40% (ie, median DOR of 9 months), versus the specific alternative hypothesis: 1 year DOR rate = 50% (ie, median DOR of 12 months), it is calculated that approximately 92 events (recurrence/progression/death) need to be observed. An estimated total of 132 responders would be required at the 3-month Visit in order to achieve 92 events. Assuming a true CRR of 60% at the 3-month Visit, approximately 220 patients would need to be enrolled in this study to observe approximately 132 responders.

If the true CRR of UGN-102 is 60% at the 3-month Visit and an initial 3-month CRR of 45% is considered as the minimum clinical benefit in this patient population, then a minimum of 116 responders out of 220 patients (observed CRR: 52.7%, 95% CI: 45.9, 59.5) will be needed so the exact 2-sided 95% CI excludes 0.45. Table 5 shows the power under different assumptions of true 3-month CRR.

Table 5 Statistical Power Scenarios

Sample Size	True 3-month CRR	Probability that the lower bound of an exact 2-sided 95% CI will exclude 0.45
220	0.60	>0.99
	0.55	0.845
	0.50	0.319

As per the informal elicitation of individual preferences of both patients and practitioners, any benefit that gives patients the chance to avoid multiple surgeries will be considered as a clinically meaningful outcome. The above minimum clinical benefits of CRR and DOR are used just for the purpose of sample size justification.

Sample size was calculated using the nQuery software.

9.3 Analysis Set

For the purposes of the analyses, the following analysis sets are defined:

Analysis Set	Description
Intent-to-treat (ITT) Analysis Set (Safety Analysis Set)	The ITT analysis set (safety analysis set), hereafter referred to as ITT analysis set, will consist of all patients who have been enrolled into the trial and who have received any instillation of UGN-102 preparation. The analysis of the primary endpoint CRR at the 3-month Visit, analyses of PRO measures, and safety analyses will be conducted using the ITT analysis set.
Per Protocol (PP) Analysis Set	The per protocol (PP) analysis set will include the subset of the patients in the ITT analysis set without major protocol deviations that would confound efficacy evaluation. All protocol deviations or conditions leading to exclusion from the PP analysis set will be detailed in the protocol deviation plan and SAP. Sensitivity analyses of the primary endpoint (CRR at 3-month Visit) may be performed using data from PP analysis set if the PP and ITT differ.
CR at 3-month Disease Assessment Analysis Set (3-month_{CR})	The CR at 3-month disease assessment (3-month_{CR}) analysis set will consist of all patients from the ITT analysis set who achieved CR at the 3-month disease assessment. This analysis set will serve as the primary analysis set for the analyses of the key secondary endpoint DOR and other secondary efficacy endpoints DFS and DCR rates at specific time points.
NCR at 3-month Disease Assessment Analysis Set (3-month_{NCR})	The NCR at 3-month disease assessment (3-month_{NCR}) analysis set will consist of all patients from the ITT analysis set who were NCR with residual disease at the 3-month disease assessment. The exploratory endpoint TTR will be analyzed using this analysis set.
NCR at Follow-up Disease Assessment Analysis Set (FUP_{NCR})	The NCR at follow-up disease assessment (FUP_{NCR}) analysis set will consist of all patients from the 3-month_{CR} analysis set who had disease recurrence or progression during the Follow-up Period. The preliminary response of these patients following the SOC treatment will be analyzed using this analysis set.

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 102) 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 or lost to follow-up or indeterminate results), the patient will be considered as an NCR for the purpose of the analysis and will be included in the denominator.

A test for binomial proportions (SAS PROC FREQ with binomial option) will be used to derive the exact two-sided 95% CI for the CR rate and using the Clopper-Pearson method (Clopper and Pearson, 1934). In addition, reasons for NCR will be tabulated using the number and percentage of patients.

Subgroup Analysis

The following subgroups will be explored in the analysis of key efficacy data provided subgroups have sufficient number of patients in each category, to result in meaningful analyses.

Subgroups will include (but 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 exact 95% CI will be presented for each of the above covariates (subgroups) using the intent-to-treat (ITT) analysis set. The summary will also be displayed by a forest plot.

9.4.3 Key Secondary Endpoint

The key secondary endpoint is 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.

The distribution of DOR will be estimated using the Kaplan-Meier method. Median time to DOR, first and third quartiles along with 95% CI (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).

DOR will be censored if no DOR event is observed before the data cut-off date of analysis or the date when a new anti-cancer therapy or another investigational treatment for cancer is started, whichever occurs earlier. The censoring date will be the date of last adequate disease assessment before either of these two dates. Further details of censoring rules will be provided in the SAP.

9.4.4 Secondary Efficacy Endpoints

Durable Complete Response at Scheduled Disease Assessment Time Points

DCR rate at scheduled disease assessment timepoints, 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 will be presented with nominal 95% exact CI (Clopper-Pearson) at each scheduled timepoint.

Disease-free Survival

DFS in patients who achieved CR at the 3-month Visit is defined as the time from first dose 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. If a patient has not had an event (recurrence or progression or death), DFS will be censored at the date of the last adequate disease assessment (ie, a visit when all scheduled disease assessments have been done). The rules for defining events and censoring will be described in the SAP.

The distribution of DFS will be estimated using the Kaplan-Meier method. Median time to DFS, first and third quartiles along with 95% CI (Brookmeyer and Crowley, 1982) will be estimated. A figure and listing of DFS will also be provided.

9.4.5 Exploratory Efficacy Endpoints

Time to Recurrence

Time to recurrence (TTR) in patients who were NCR (residual disease) at the 3-month Visit is defined as the time from the date of first treatment after NCR to the earliest date of recurrence or progression as determined using the date of cystoscopy, for cause biopsy, or cytology, whichever occurred first. If a patient has not had an event (recurrence or progression), TTR will be censored at the date of the last adequate disease assessment (ie, a visit when all scheduled disease assessments have been done) after the date of first treatment after NCR. The rules for defining events and censoring will be described in the SAP.

The distribution of TTR will be estimated using the Kaplan-Meier method. Median time to TTR, first and third quartiles along with 95% CI (Brookmeyer and Crowley, 1982) will be estimated. A figure and listing of TTR will also be provided.

Other Efficacy Analyses

Preliminary responses following SOC treatment in 3-month CR patients who have disease recurrence or progression during the Follow-up Period will be summarized descriptively.

In addition, the impact of UGN-102 on subsequent SOC treatment in patients who have NCR at the 3-month Visit or disease recurrence/progression during the Follow-up Period will be analyzed using the proportion of patients whose planned NMIBC treatment at baseline was downgraded following treatment with UGN-102 (eg, from TURBT to biopsy and/or fulguration).

Further details will be provided in the SAP.

9.4.6 Safety Analysis

Safety analyses will be conducted using the ITT 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.

The overall observation period will be divided into three mutually exclusive time periods:

1. Pre-treatment period: from day of patient's informed consent to the day before administration of first treatment
2. Up to 3 months: from day of first treatment administration to 3-month Visit
3. Post 3 months: after the 3-month Visit until the end of study

Adverse Events and Serious Adverse Events

Summary tables for AEs will include only AEs that started or worsened during the study (ie, up to 3 months and post 3 months periods), the 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, 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. For some events, several AE preferred terms may be 'collapsed.' The list of terms to be used for each category of AESI may be based on the Safety Review Team

agreements in place at the time of reporting. The Safety Review Team 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 events. 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.

The following summaries will be generated separately for hematology, biochemistry, and urinary laboratory tests as appropriate:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high)
- classification to compare baseline to the worst on-treatment value.
- listing of all or selected laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above-mentioned tables and listings, other exploratory analyses, for example figures plotting time course of raw or change in laboratory tests over time or box plots, might be generated 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.

9.4.7 Patient-Reported Outcome Measures

An exploratory objective of the study is to assess the effect of treatment with UGN-102 on PRO measures. The PRO assessment plan includes the EORTC questionnaires for cancer patients (QLQ-C30) (Appendix 2) and patients with NMIBC (QLQ-NMIBC24) (Appendix 3). Analyses will be based on the ITT 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 scoring manuals for each respective patient questionnaires' standard scoring guidelines (Fayers et al, 2001; Blazeby et al, 2014). 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 QLQ-NMIBC24 questionnaires. Full details of all of the health outcomes analyses will be provided in the SAP.

9.4.8 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 actual time point of the primary analysis will be determined based on the emerging data.

The EOS analysis will be performed after all patients complete the study, are withdrawn from the study, are lost to follow-up, or when the study is closed by the Sponsor. Primary results of all relevant endpoints will be updated using the final data.

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 are required before initiating any study procedures and starting treatment/administering 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 Safety Review Team.

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 are 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 CRF.

Guidance on completion of eCRFs will be provided in the CRF 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 provided guidance.

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 is 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 FDA.

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 clinical study report (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

American Cancer Society (ACS). Cancer Facts & Figures 2021. Atlanta, GA, USA: American Cancer Society; 2021.

American Society of Anesthesiologists (ASA). ASA Physical Status Classification System. https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. Updated December 13, 2020. Accessed June 9, 2021.

Avallone MA, Sack BS, El-Arabi A, et al. Ten-year review of perioperative complications after transurethral resection of bladder tumors: analysis of monopolar and plasmakinetic bipolar cases. J Endourol. 2017;31(8):767-773.

Babjuk M, Burger M, Compérat EM, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) - 2019 update. Eur Urol. 2019;76(5):639-657.

Balbay MD, Cimentepe E, Unsal A, Bayrak O, Koç A, Akbulut Z. The actual incidence of bladder perforation following transurethral bladder surgery. J Urol. 2005;174(6):2260-2263.

Blazeby JM, Hall E, Aaronson NK, et al. Validation and reliability testing of the EORTC QLQ-NMIBC24 questionnaire module to assess patient-reported outcomes in non-muscle-invasive bladder cancer. Eur Urol. 2014;66(6):1148-1156.

Brookmeyer R, Crowley J. A confidence interval for the median survival time. Biometrics. 1982;38:29-41.

Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol. 2016;196:1021.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26(4):404-413.

Colombo R, Rocchini L, Suardi N, et al. Neoadjuvant short-term intensive intravesical mitomycin C regimen compared with weekly schedule for low-grade recurrent non-muscle-invasive bladder cancer: preliminary results of a randomised phase 2 study. Eur Urol. 2012;62(5):797-802.

Common Terminology Criteria for Adverse Events (CTCAE). Version 5.0. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Published November 27, 2017. Accessed July 23, 2020.

Daneshmand S, Patel S, Lotan Y, et al. Efficacy and safety of blue light flexible cystoscopy with hexaminolevulinate in the surveillance of bladder cancer: a phase III, comparative, multicenter study. J Urol. 2018;199(5):1158-1165.

De Nunzio C, Franco G, Cindolo L, et al. Transuretral resection of the bladder (TURB): analysis of complications using a modified Clavien system in an Italian real life cohort. Eur J Surg Oncol. 2014;40(1):90-95.

Erikson MS, Petersen AC, Andersen KK, Jacobsen FK, Mogensen K, Hermann GG. Do repeated transurethral procedures under general anesthesia influence mortality in patients with non-invasive urothelial bladder cancer? A Danish national cohort study. Scand J Urol. 2020;54(4):281-289.

Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. EORTC QLQ-C30 Scoring Manual (3rd Edition). Brussels: EORTC, 2001.

Ghali F, Moses RA, Raffin E, Hyams ES. What factors are associated with unplanned return following transurethral resection of bladder tumor? An analysis of a large single institution's experience. Scand J Urol. 2016;50(5):370-373.

Hollenbeck BK, Miller DC, Taub D, et al. Risk factors for adverse outcomes after transurethral resection of bladder tumors. Cancer. 2006;106(7):1527-1535.

Hurle R, Lazzeri M, Vanni E, et al. Active Surveillance for Low Risk Nonmuscle Invasive Bladder Cancer: A Confirmatory and Resource Consumption Study from the BIAS Project. J Urol. 2018;199(2):401-406.

Jung A, Nielsen ME, Crandell JL, et al. Health-related quality of life among non-muscle-invasive bladder cancer survivors: a population-based study. BJU Int. 2020;125(1):38-48.

Kamat AM, Witjes JA, Brausi M, et al. Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. J Urol. 2014;192(2):305-315.

Lindgren MS, Bue P, Azawi N, et al. The DaBlaCa-13 Study: short-term, intensive chemoresection versus standard adjuvant intravesical instillations in non-muscle-invasive bladder cancer-a randomised controlled trial. Eur Urol. 2020;78(6):856-862.

Marcq G, Hénon F, Ouzaid I, Fantoni JC, Hermieu JF, Xylinas E. Active surveillance for non-muscle invasive bladder cancer. Transl Androl Urol. 2019;8(1):54-60.

Matulewicz RS, Sharma V, McGuire BB, Oberlin DT, Perry KT, Nadler RB. The effect of surgical duration of transurethral resection of bladder tumors on postoperative complications: an analysis of ACS NSQIP data. Urol Oncol. 2015;33(8):338.e19-24.

Miyake M, Fujimoto K, Hirao Y. Active surveillance for nonmuscle invasive bladder cancer. Investig Clin Urol. 2016;57(Suppl 1):S4-S13.

Monteiro LL, Witjes JA, Agarwal PK, et al. ICUD-SIU International Consultation on Bladder Cancer 2017: management of non-muscle invasive bladder cancer. World J Urol. 2019;37(1):51-60.

Mostafid AH, Porta N, Cresswell J, et al. CALIBER: a phase II randomized feasibility trial of chemoablation with mitomycin-C vs. surgical management in low-risk non-muscle-invasive bladder cancer. BJU Int. 2020;125(6):817-826.

National Comprehensive Cancer Network (NCCN). Bladder Cancer (Version 4.2021). https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Updated July 27, 2021. Accessed September 15, 2021.

Nolte S, Liegl G, Petersen MA, et al. General population normative data for the EORTC QLQ-C30 health-related quality of life questionnaire based on 15,386 persons across 13 European countries, Canada and the Unites States. Eur J Cancer. 2019;107:153-163.

Parisse T, Reines K, Basak R, Mueller D, Smith A. Patient perception of transurethral resection of bladder tumor vs. chemoablation for non-muscle invasive bladder cancer treatment. J Urol. 2021;206(3S Suppl):e301-e302.

Patel HD, Ball MW, Cohen JE, Kates M, Pierorazio PM, Allaf ME. Morbidity of urologic surgical procedures: an analysis of rates, risk factors, and outcomes. Urology. 2015;85(3):552-559.

Pereira JF, Pareek G, Mueller-Leonhard C, et al. The perioperative morbidity of transurethral resection of bladder tumor: implications for quality improvement. Urology. 2019;125:131-137.

Rambachan A, Matulewicz RS, Pilecki M, Kim JY, Kundu SD. Predictors of readmission following outpatient urological surgery. J Urol. 2014;192(1):183-188.

Rutherford C, Costa DSJ, King MT, Smith DP, Patel MI. A conceptual framework for patient-reported outcomes in non-muscle invasive bladder cancer. Support Care Cancer. 2017;25(10):3095-3102.

Scott NW, Fayers PM, Aaronson NK, et al, on behalf of the EORTC Quality of Life Group. EORTC QLQ-C30 Reference Values. https://www.eortc.org/app/uploads/sites/2/2018/02/reference_values_manual2008.pdf. Updated July 2008. Accessed October 6, 2021.

Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 21 Regs Research Data, Limited Field Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2018 Sub (2000-2016) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2017 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2019, based on the November 2018 submission.

Yu EY, Nekeman D, Billingham LJ, et al. Health-related quality of life around the time of diagnosis in patients with bladder cancer [published correction appears in BJU Int. 2020 Nov;126(5):646]. BJU Int. 2019;124(6):984-991.

Appendix 1. Guidance on Evaluation of Response

Response will be evaluated based on visual evaluation 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 or every 6 months thereafter during the Follow-up Period.

CR (Complete Response): A patient will be considered to have CR if there is No Detectable Disease (NDD) in the bladder by cystoscopy, biopsy (if indicated) and urine cytology.

NCR (Non-complete Response) at 3-month disease assessment: There is evidence of disease under study.

Recurrence (at follow-up visits): There is evidence of disease under study. 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, 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 8 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 (No Detectable Disease).

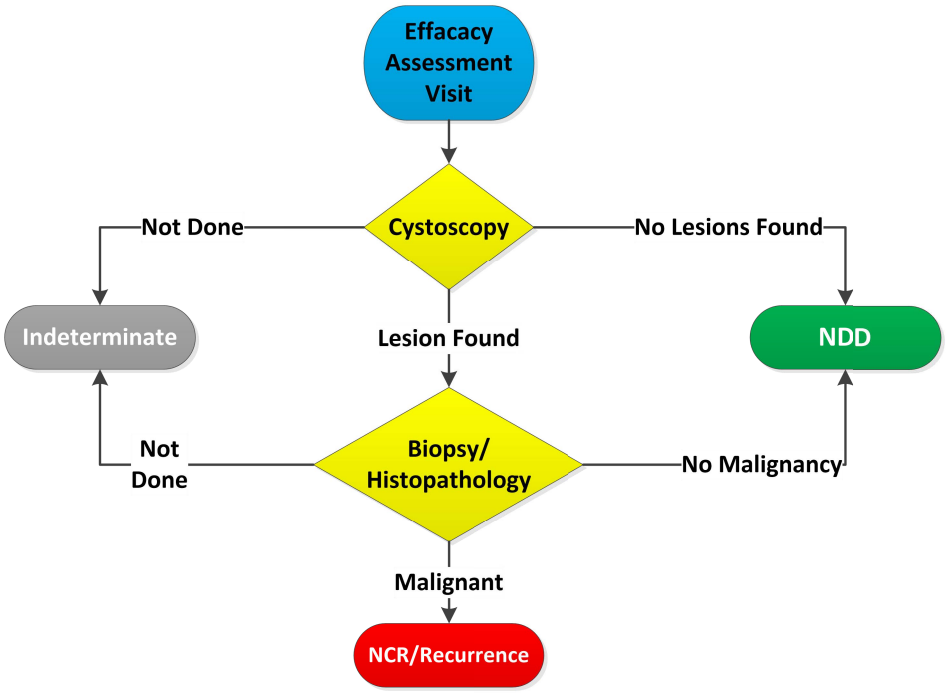
c. If cystoscopy was not performed and/or the biopsy was not done when indicated, the evaluation will be indeterminate.

Table 6 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

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 urothelial carcinoma of the upper tract (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, 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 7 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

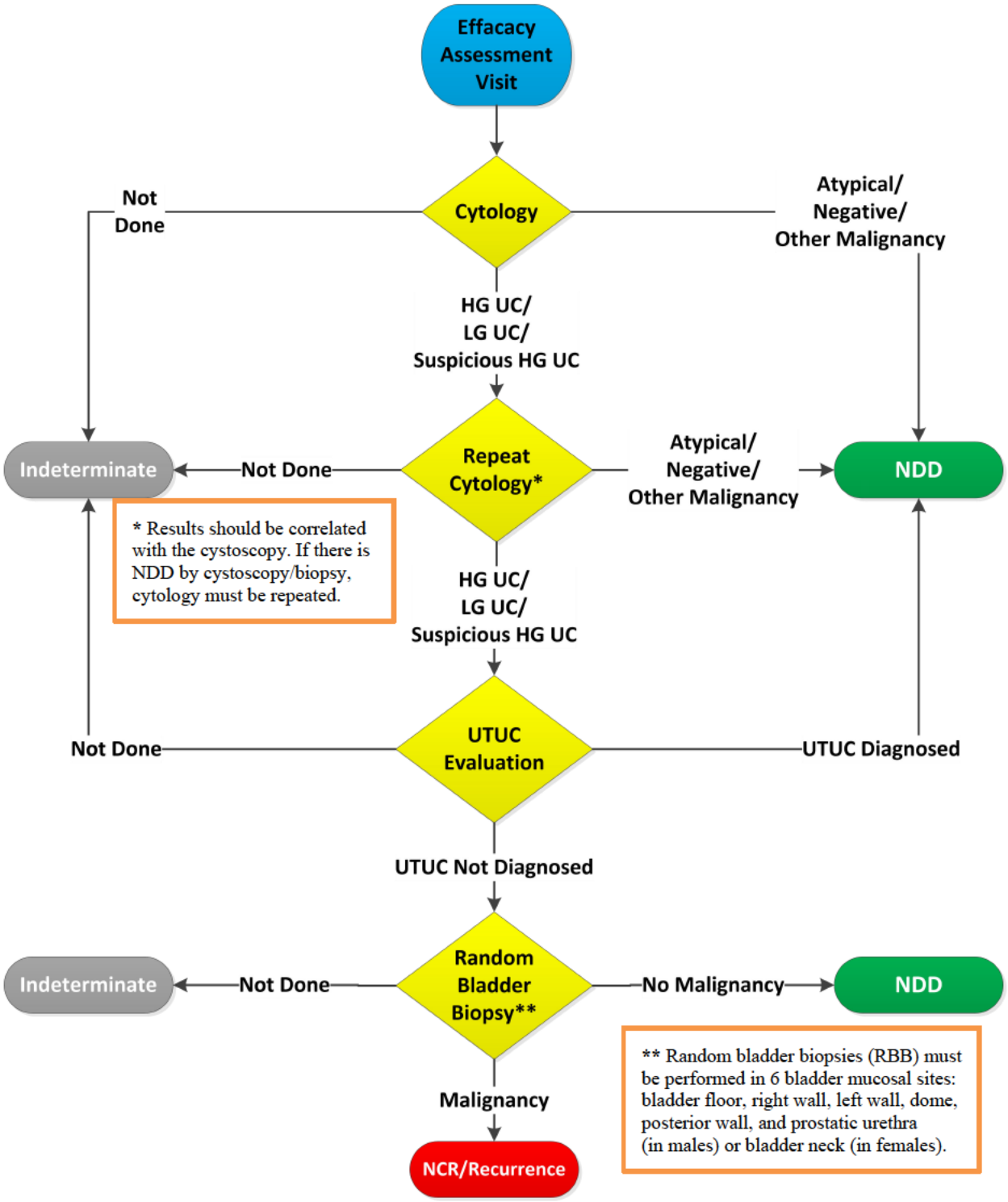
HG = high grade; LG = low grade; NA = not applicable; NCR = non-complete response; NDD = no detectable disease; UC = urothelial carcinoma; UTUC = upper tract urothelial carcinoma.

[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.

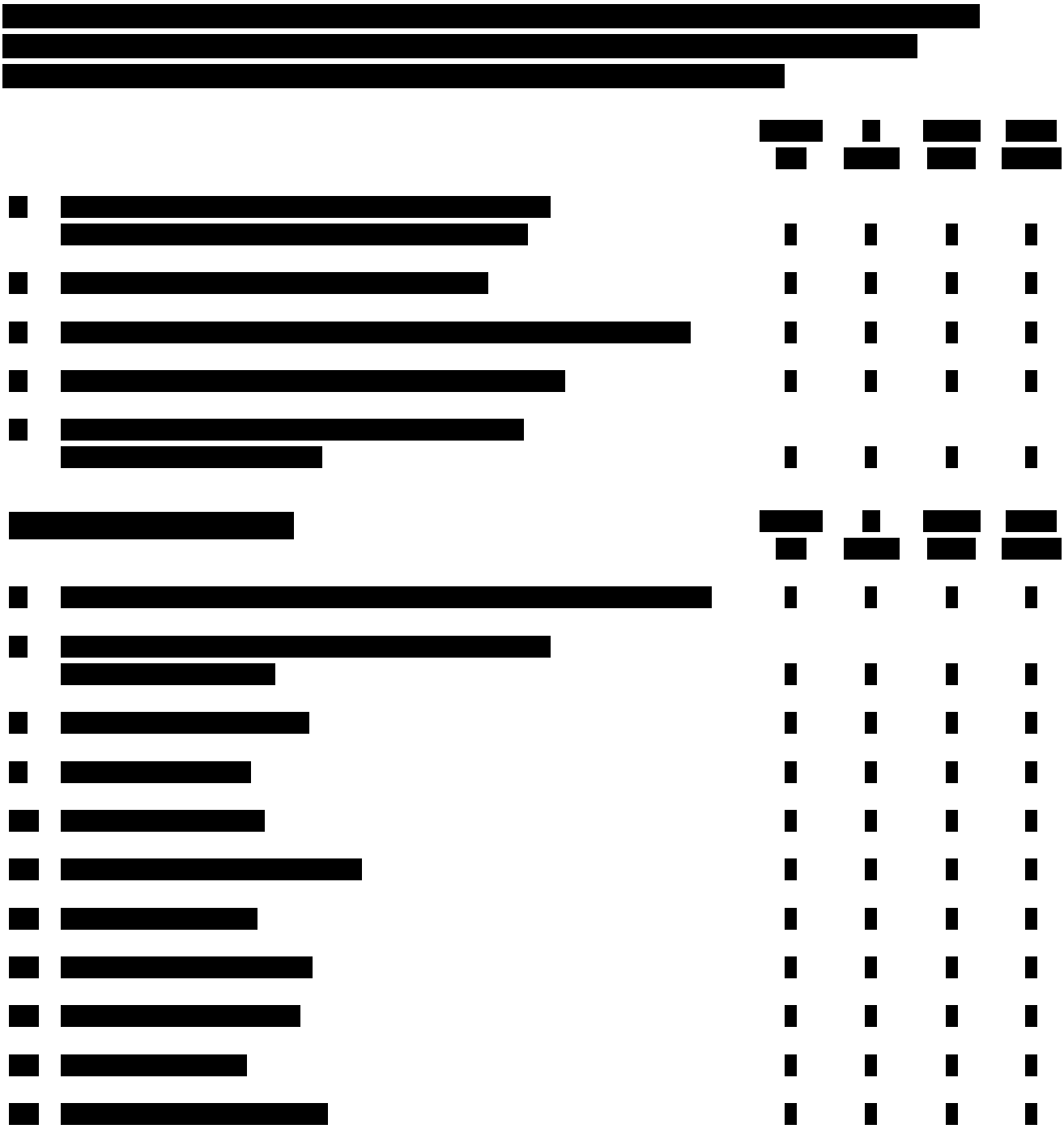
Table 8 Evaluation of Response Based on All Assessments

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

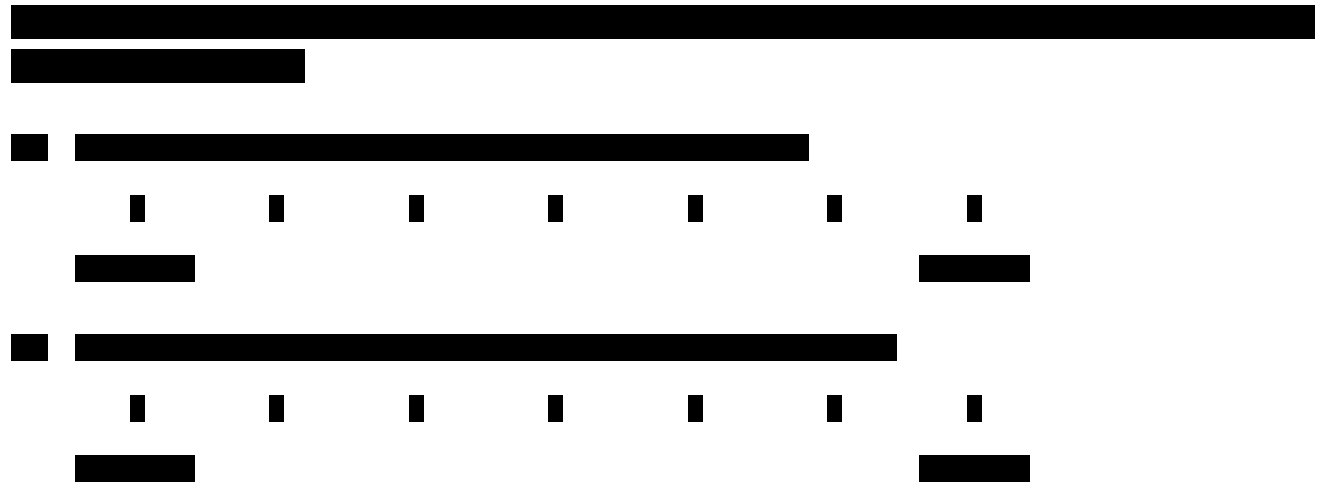
CR = complete response; CRF = case report form; NCR = non-complete response; NDD = no detectable disease; UTUC = upper tract urothelial carcinoma.

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

Appendix 2. EORTC QLQ-C30



Please go on to the next page



Appendix 3. EORTC QLQ-NMIBC24

[redacted]

Please go on to the next page

[redacted]

[redacted]

Appendix 4. Protocol Revision History

Version	Date	Description of Changes	Brief Rationale
5.0	28 Feb 2024	• Added expected content of the EU CTR to the following sections: title page, compliance statement, and Sections 6.2.1, 6.5, 7, 8.1.6, 8.2.3, 8.3.1.1, 8.3.5, 10.1.1, 10.1.3.2, 10.1.4, 10.1.5, 10.1.6, 10.1.12, and 10.1.15 • Updated key roles and contact information • Revised Labcorp to Fortrea • Clarified in Section 9.4.5 that TTR will be estimated using the Kaplan-Meier method • Clarified in Section 9.4.6 that the overall observation period for safety will be divided into 3 time periods: pre-treatment, up to 3 months, and post 3 months • Other minor revisions and formatting changes have been made throughout the document	[redacted]
4.0	04 May 2022	• Added exclusion criteria for patients with other active malignancy requiring treatment with systemic anticancer therapy and patients with other medical or surgical condition that could compromise patient safety or the interpretation of study results • Clarified that concomitant treatment with systemic anticancer therapy (eg, chemotherapy, immunotherapy, radiation therapy) is prohibited	[redacted]

Version	Date	Description of Changes	Brief Rationale
3.0	20 Apr 2022	• Updated key roles and contact information	[redacted]
		• Added an exclusion criterion for patients who have previously participated in a study in which they received UGN-102	[redacted]
		• Clarified that general physical examinations will be performed by licensed personnel at the investigative site	[redacted]
		• Removed rectal examination and bimanual examination from list of required procedures at Screening	[redacted]
		• Removed pre- or post-operative non-study chemotherapy and added TURBT as prohibited concomitant medication / procedure	[redacted]
		• Clarified circumstances that may necessitate use of the site's local laboratory for protocol specified laboratory tests	[redacted]
		• Revised Section 8.3.7 (Pregnancy) to state that details of pregnancies will be collected from the start of study treatment to 6 months after the last dose of UGN-102	[redacted]
		• Other minor revisions have been made throughout the protocol	[redacted]
2.0	21 Dec 2021	• Updated key roles and contact information	[redacted]
		• Revised the exclusion criterion of past or current T1 bladder cancer to current tumor grading of T1	[redacted]
		• Replaced the study schema	[redacted]
		• Minor revisions to the schedule of activities	[redacted]