Title Page

Protocol Title: A Randomized, Controlled, Open-label Study of the Efficacy, Durability, and Safety of UGN-102 With or Without TURBT in Patients with Low Grade Intermediate Risk Non-Muscle Invasive Bladder Cancer (LG IR-NMIBC) (ATLAS)

Protocol Number: BL006

Compound: UGN-102 (mitomycin) for intravesical solution

Brief Title: A Phase 3 Study of UGN-102 for Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer (ATLAS)

Study Phase: 3

Sponsor Name: UroGen Pharma Ltd.

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Regulatory Agency Identifier Number(s):
IND: 138749
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Statement of Compliance

The study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP) and the applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator 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), recruitment materials, and all patient materials will be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for review and approval. 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.

Notification of Early Study Enrollment Closure (10 Nov 2021)

UroGen Pharma Ltd. (Sponsor) closed enrollment in Study BL006 on 10 Nov 2021 in order to pursue an alternative development strategy for UGN-102 in patients with low grade intermediate risk non-muscle invasive bladder cancer (LG IR NMIBC). This decision was not based on new information about the efficacy or safety of UGN-102, and UGN-102 continues to have a favorable benefit-risk profile that supports its continued development for treatment of LG IR NMIBC. Patients who provided written informed consent to participate in Study BL006 on or before 10 Nov 2021 are permitted to continue their study participation according to the study protocol.

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Controlled, Open-label Study of the Efficacy, Durability, and Safety of UGN-102 With or Without TURBT in Patients with Low Grade Intermediate Risk Non-Muscle Invasive Bladder Cancer (LG IR-NMIBC) (ATLAS)

Brief Title: A Phase 3 Study of UGN-102 for Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer (ATLAS)

Overall Design: This study is a global, randomized, controlled, open-label Phase 3 study designed to assess the long-term efficacy and safety of UGN-102 (mitomycin) for intravesical solution (i.e., intravesical instillation) with or without Transurethral Resection of Bladder Tumors (TURBT) vs. TURBT alone in the treatment of patients with LG IR-NMIBC.

Eligible patients who have signed the informed consent and met all study entry criteria will be randomized in a 1:1 ratio to UGN-102 with or without TURBT or TURBT alone. Patients randomized to the UGN-102 group will receive 6 weekly intravesical instillations of UGN-102 followed by TURBT only if needed and patients randomized to the TURBT alone group will undergo TURBT followed by repeat TURBT if needed.

All patients will return to the clinic at approximately 3 months from the initiation of treatment for determination of response to treatment. Following this initial evaluation, all patients confirmed to have had a complete response (CR) will receive no further treatment and will enter the follow-up period of the study. Patients confirmed to have had a non-complete response (NCR) in either treatment arm will undergo TURBT of any remaining lesions and will then also enter the follow-up period of the study. **Note:** If the Investigator determines that a formal TURBT in the operating room is unnecessary following cystoscopy and biopsy of remaining lesions (e.g., residual disease can be addressed by in office biopsy and/or fulguration), such an alternative procedure is permitted based on the Investigator's medical judgment.

Disease-free survival (DFS) is the primary endpoint of this study. During the follow-up period, patients will return to the clinic quarterly until the end of their participation in the study to determine if they remain disease free. Patients determined to be disease free will remain on study until completion of all their follow-up visits (approximately 24 months from the onset of treatment) or until disease recurrence, disease progression, or death is documented, whichever comes first. Patients determined to have had a protocol-defined recurrence or progression at any follow-up or unscheduled visit will be considered to have completed the study and released to the care of their treating physician.

Objectives and Endpoints

OBJECTIVE	ENDPOINT
Primary	
To evaluate the efficacy of UGN-102 with or without TURBT versus TURBT alone with respect to disease-free survival (DFS) in patients with Low Grade Intermediate Risk Non-Muscle Invasive Bladder Cancer (LG IR-NMIBC).	Disease-free survival (DFS) is defined as the time from randomization until the earliest date of any of the following events: • Failure to be rendered free of local disease at the 3-Month assessment after the TURBT procedure. • Recurrence of low-grade disease after the 3-Month assessment (i.e., during the follow-up period). • Progression to high-grade disease. • Death due to any cause.
Secondary	
1. To evaluate the efficacy of UGN-102 with or without TURBT versus TURBT alone with respect to: a) Time to Recurrence (TTR) b) Complete Response Rate (CRR) at 3-Month disease assessment c) Duration of Response (DOR) d) Avoidance of surgery (TURBT) for treatment of LG IR-NMIBC 2. To evaluate the safety profile of UGN-102 with or without TURBT versus TURBT alone. 3. To assess the effect of UGN-102 with or without TURBT versus TURBT alone on Patient Reported Outcomes (PROs) including disease related symptoms, functioning, and health-related quality of life (HRQoL). 4. To evaluate visit level Complete Response Rate (CRR)	1. The following efficacy endpoints will be evaluated: a) Time to recurrence (TTR) is defined as the time from randomization until the earliest date of recurrence of low-grade disease or progression to high-grade disease. b) Complete response rate (CRR), defined as the proportion of patients who achieved CR at the 3-Month disease assessment. c) Duration of response (DOR), defined as the time from first documented CR until the earliest date of any of the following events: • Recurrence of low-grade disease. • Progression to high-grade disease. • Death due to any cause. d) Proportion of patients requiring TURBT in each arm and average number of TURBT interventions per patient in each arm 2. The safety profile of UGN-102 and TURBT will be evaluated as assessed through standard clinical and laboratory tests (hematology and chemistry, urinalysis, physical examination, vital sign measurements, diagnostic tests, etc.) and through the collection of reports of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest. 3. Changes from baseline in HRQoL measures assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Non-muscle Invasive Bladder Cancer patients (EORTC-QLQ-NMIBC24). 4. Observed CRR at scheduled disease assessment timepoints, defined as the proportion of patients who had CR at 3-Month disease assessment and maintained CR up to that particular follow-up disease assessment.

OBJECTIVE	ENDPOINT
Exploratory	
To explore potential differences in health resource utilization with UGN-102 vs TURBT in patients with LG NMIBC	Number of patients hospitalized for non-elective reasons, total number and length of non-elective hospitalizations

Inclusion Criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. Patient must be ≥ 18 years of age, at the time of signing the informed consent.
3. Patient who has newly diagnosed or historic LG NMIBC (Ta) histologically confirmed by cold cup biopsy at screening or within 8 weeks of screening;
4. Is at intermediate risk for progression, defined as having 1 or 2 of the following:
   a. presence of multiple tumors
   b. solitary tumor > 3 cm
   c. recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis at initial Screening Visit)
5. Negative voiding cytology for high grade (HG) disease within 6 weeks of screening;
6. 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) (Serum glutamic oxaloacetic transaminase [SGOT])/Alanine aminotransferase (ALT) (Serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × ULN
   - Alkaline phosphatase (ALP) ≤ 2.5 × ULN
   - Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min;
7. Has no evidence of active urinary tract infection (UTI);
8. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Exclusion Criteria:

1. History of carcinoma in situ (CIS) on preliminary cystoscopy within 5 years of enrollment;
2. Received Bacille de Calmette et Guérin (BCG) treatment for urothelial carcinoma (UC) within previous 1 year;

3. History of HG papillary UC in the past 2 years;
4. Known allergy or sensitivity to mitomycin that in the Investigator's opinion cannot be readily managed;
5. Clinically significant urethral stricture that would preclude passage of a urethral catheter;
6. History of pelvic radiotherapy;
7. History of:
   a. neurogenic bladder
   b. active urinary retention
   c. any other condition that would prohibit normal voiding
8. Past or current muscle invasive (i.e., T2, T3, T4) or metastatic UC or concurrent upper tract urothelial carcinoma (UTUC);
9. Current tumor grading of T1;
10. 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;
11. History of prior treatment with an intravesical chemotherapeutic agent except for a single dose of chemotherapy immediately post any previous TURBT;
12. Has previously participated in a study in which they received UGN-102;
13. Has participated in a study with an investigational agent or device within 30 days of randomization.

Brief Summary: This is a global, randomized, controlled, open-label phase 3 study of UGN-102 with or without TURBT vs. TURBT alone in the treatment of patients with LG IR-NMIBC. Patients will either receive 6 weekly intravesical instillations of UGN-102 followed by TURBT only if needed or will undergo TURBT followed by repeat TURBT if needed. Disease-free survival is the primary endpoint of this study. Patients will be followed long-term for disease recurrence until the end of their participation in the study (i.e., until completion of all follow-up visits or until disease recurrence, disease progression, or death is documented).

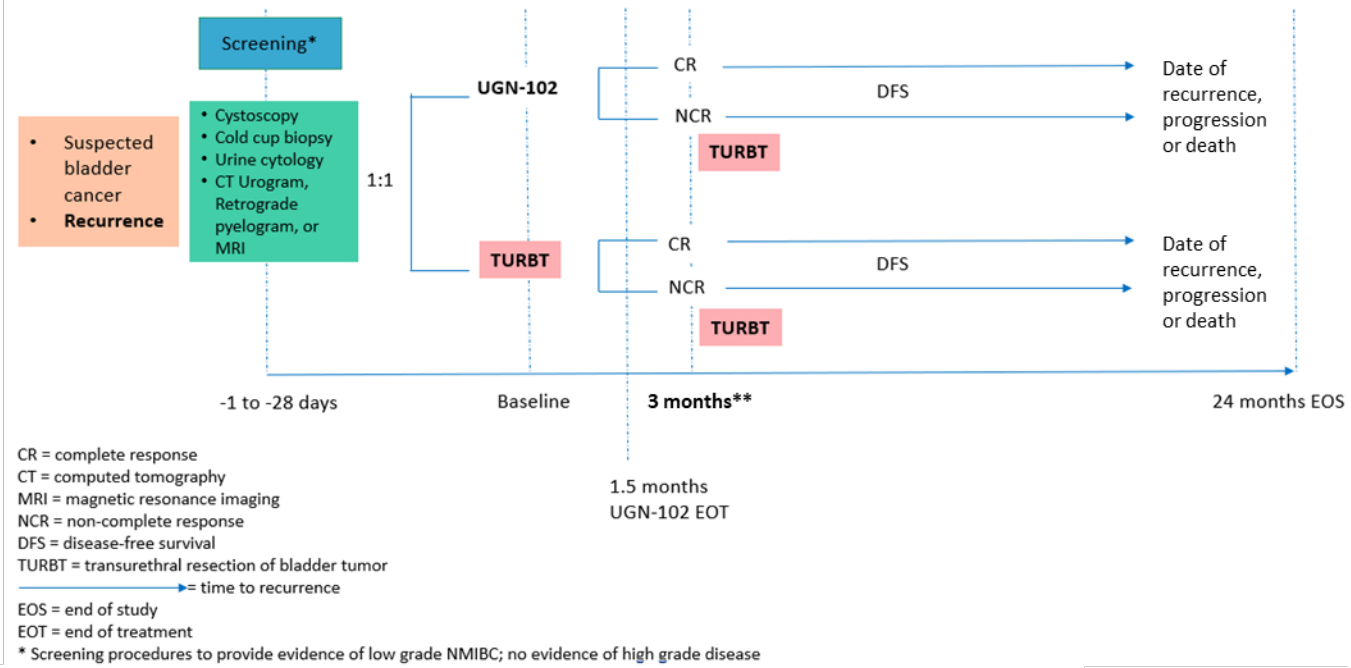
Number of Patients: The enrollment of this study has been stopped prematurely by the Sponsor in order to pursue an alternative development strategy for UGN-102 in the same patient population; 282 eligible patients who were screened on or before 10 Nov 2021 were randomized in this study. The study will be conducted primarily by appropriately trained urologists at approximately 120 investigative study sites in the United States, Israel, and Europe who provide care to patients with bladder cancer.

Intervention Groups and Duration: 1. UGN-102 (75 mg via intravesical instillation starting at Day 1 X 6 weeks) ± TURBT for NCR patients; 2. TURBT alone (Day 1) ± repeat TURBT for NCR patients.

Data Review Committee: Not applicable.

1.2. Schema

UGN-102-Ph3-bladder cancer study scheme



CR = complete response
CT = computed tomography
MRI = magnetic resonance imaging
NCR = non-complete response
DFS = disease-free survival
TURBT = transurethral resection of bladder tumor
→ = time to recurrence
EOS = end of study
EOT = end of treatment
* Screening procedures to provide evidence of low grade NMIBC; no evidence of high grade disease

**Patients confirmed to have a disease progression at the 3-month Visit will be discontinued from the study and managed according to best practice (i.e., SoC) by their treating physician

1.3. Schedule of Activities (SoA) – Phase 3 Bladder UGN-102 Patient

Procedures	Screening Period	Treatment Period							WP	3-M DAV	FUP (Follow-up visits start at Month 6 and continue every 3 months thereafter until completion of all follow-up visits or recurrence/progression/death is documented) [a]									Un-scheduled
	Screening/ Randomization [b]	Treatment Visit [c]	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Telephone Contact	Waiting Period	Assessment Visit [d]	Telephone Contact	Telephone Contact	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit (EOS)	Unscheduled Visit [e]
Visit	1	2a	2b	2c	2d	2e	2f	TC M1	n/a	3	TC M2	TC M3	4	5	6	7	8	9	10	n/a
Day/Week/Month	D-28 to D0	D1/ W1	D8/ W2	D15/ W3	D22/ W4	D29/ W5	D36/ W6	M2	W7 to W13	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24	n/a
Window	n/a	D0 +0/+28 d	-1/+3 d	-1/+3 d	-1/+3 d	-1/+3 d	-1/+3 d	±1 wk	n/a	±1 wk	±1 wk	±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	± 2 wks	n/a
Informed consent	X																			
Inclusion and exclusion criteria	X																			
Demographics	X																			
QLQ-NMIBC24	X [f]	X	X	X	X	X	X			X			X	X	X	X	X	X	X	X
Medical/Surgical and Smoking History	X																			
Concomitant medication review (incl. any past therapy related to urothelial CA)	X [g]	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
General physical examination	X																			
Urological Exam	X [h]	X	X	X	X	X	X													
Height	X																			
Weight	X									X										
Vital signs	X	X	X	X	X	X	X			X			X	X	X	X	X	X	X	X
Hematology/ Serum Chemistry (central laboratory)	X	X	X	X	X	X	X			X			X							
Urinalysis [i]	X	X	X	X	X	X	X			X			X	X	X	X	X	X	X	X
Pregnancy test [j] (WOCBP only)	X	X								X [k]										

Procedures	Screening Period	Treatment Period							WP	3-M DAV	FUP (Follow-up visits start at Month 6 and continue every 3 months thereafter until completion of all follow-up visits or recurrence/progression/death is documented) [a]									Un-scheduled
	Screening/ Randomization [b]	Treatment Visit [c]	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Treatment Visit	Telephone Contact	Waiting Period	Assessment Visit [d]	Telephone Contact	Telephone Contact	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit (EOS)	Unscheduled Visit [e]
Visit	1	2a	2b	2c	2d	2e	2f	TC M1	n/a	3	TC M2	TC M3	4	5	6	7	8	9	10	n/a
Day/Week/Month	D-28 to D0	D1/ W1	D8/ W2	D15/ W3	D22/ W4	D29/ W5	D36/ W6	M2	W7 to W13	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24	n/a
Window	n/a	D0 +0/+28 d	-1/+3 d	-1/+3 d	-1/+3 d	-1/+3 d	-1/+3 d	±1 wk	n/a	±1 wk	±1 wk	±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	± 2 wks	n/a
Adverse events [l] (incl. telephone calls at M2, M4, M5 ± 1 week)	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X
CT Urogram, retrograde pyelogram or MRI [m]	X																			
Cystoscopy (white light)	X									X			X	X	X	X	X	X	X	X
Voiding urine cytology (send to central pathology) [n]	X									X			X	X	X	X	X	X	X	X
Cold cup biopsy (send to central pathology) [o]	X																			
Randomization	X																			
Drug administration		X	X	X	X	X	X													
Biopsy remaining lesions if indicated (send to central pathology)										X			X	X	X	X	X	X	X	X
Complete eCRFs	X	X	X	X	X	X	X			X			X	X	X	X	X	X	X	X
TURBT [p]										X										

Abbreviations: 3-M DAV = 3-Month disease assessment visit; AE = adverse event; CA = cancer; CT = computed tomography; d = day; D= Visit Day; eCRF =electronic case report form; EOS = end-of-study; FUP = Follow-up Period; ICF = informed consent form; LG = low grade; M = month; MRI = magnetic resonance imaging; n/a = not applicable; NCR = Non-complete response; SAE = serious adverse event; TCM = telephone contact month; TURBT = Transurethral Resection of Bladder Tumor; QLQ-NMIBC24 = Quality of Life Questionnaire for NMIBC; UGN-102 = UGN-102 (mitomycin) for intravesical solution; UTUC = upper tract urothelial carcinoma; W = Week: wks = weeks; WOCBP = women of child-bearing potential; WP = Waiting Period.

Notes: Primary disease assessment/response evaluation will be performed at the post 3-Month visits in the Follow-up Period.

a. For those patients in the follow-up period who have a disease recurrence or progression, the EOS Visit needs to be completed.
b. The screening period is up to 14 days for patients that do not need a screening biopsy and up to 28 days for patients that need a screening biopsy (see Section 8.1.1). Randomization 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. Screening procedures are to provide evidence of low grade NMIBC and no evidence of high grade disease.
c. Windows are provided to accommodate patient logistics in scheduling. In any case, instillations should not occur more frequently than 6 days apart. Day 1 does not necessarily need to be the day after Day 0 e.g., in the event additional time is required to initiate treatment due to logistics such as scheduling procedure or training for UGN-102 instillation. Every effort should be made to minimize the time interval between diagnosis and treatment.
d. Patients who discontinue from the study before the 3-Month Visit should have all assessments specified for the EOS Visit as their EOS assessments.
e. If an unscheduled visit is required, assessments should be performed as appropriate to the needs of the visit, although safety assessments should be performed, if feasible.
f. For baseline score.
g. Any past therapy (e.g. medical or surgical interventions) related to urothelial cancer will be recorded during Screening.
h. Performed prior to cystoscopy at Screening. See Section 8.3.1 for details.
i. Dipstick on-site; culture and sensitivity added at screening if positive for infection (at local laboratory).
j. Urine or serum pregnancy test (at local laboratory).
k. Pregnancy test at assessment visit for NCR patients who will undergo TURBT.
l. 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 Month-6 visit (Visit 4). Subsequent to the Month-6 visit, all SAEs (regardless of causality) and non-serious AEs assessed as related to study treatments (UGN-102 or TURBT) or study procedures should be collected until the EOS Visit.
m. CT Urogram, retrograde pyelogram, or MRI (if other tests are contraindicated) to rule out UTUC (acceptable if performed within 6 months of initial Screening Visit) (results assessed locally).
n. No cytology needed if results from a prior cytology within 6 weeks of initial Screening Visit are available.
o. Cold cup biopsy to confirm LG tumor performed only if not already performed within 8 weeks of initial Screening Visit. This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of tumor is not to be performed.
p. NCR patients at the 3-Month Visit will receive TURBT and enter the FUP. TURBT will be scheduled as soon as possible at Month 3 and every attempt should be made to perform TURBT within 1 month of this visit. **Note:** If the Investigator determines that a formal TURBT in the operating room is unnecessary following cystoscopy and biopsy of remaining lesions (e.g., residual disease can be addressed by in office biopsy and/or fulguration), such an alternative procedure is permitted based on the Investigator's medical judgment.

1.4. Schedule of Activities (SoA) – Phase 3 Bladder TURBT Patient

Procedures	Screening Period	Treatment Period	Waiting Period	Follow-up Period		3-M DAV	Follow-up Period (Follow-up visits start at Month 6 and continue every 3 months thereafter until completion of all follow-up visits or recurrence/progression/death is documented)[a]									Unscheduled
	Screening/ Randomization[b]	Treatment Visit[c]	Waiting Period	Telephone Contact	Telephone Contact	Assessment Visit[d]	Telephone Contact	Telephone Contact	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit (EOS)	Unscheduled Visit[e]
Visit	1	2	n/a	TCM1	TCM2	3	TCM3	TCM4	4	5	6	7	8	9	10	n/a
Day/Week/Month	D-28 to D0	D1/W1	W2 to W13	M1	M2	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24	n/a
Window	n/a	D0 +0/+28 d	n/a	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	n/a
Informed consent	X															
Inclusion and exclusion criteria	X															
Demographics	X															
QLQ-NMIBC24	X[f]	X				X			X	X	X	X	X	X	X	X
Medical/Surgical and Smoking History	X															
Concomitant medication review (incl. any past therapy related to urothelial CA)	X[g]	X		X	X	X	X	X	X	X	X	X	X	X	X	X
General physical examination	X															
Urological Exam	X[h]	X														
Height	X															
Weight	X					X										
Vital signs	X	X				X			X	X	X	X	X	X	X	X
Hematology/ Serum chemistry (central laboratory)	X	X				X			X							
Urinalysis[i]	X	X				X			X	X	X	X	X	X	X	X
Pregnancy test[j] (WOCBP only)	X	X				X[k]										
Adverse events[l] (incl. telephone calls at M1, M2, M4, M5 ± 1 week)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures	Screening Period	Treatment Period	Waiting Period	Follow-up Period		3-M DAV	Follow-up Period (Follow-up visits start at Month 6 and continue every 3 months thereafter until completion of all follow-up visits or recurrence/progression/death is documented)[a]									Unscheduled
	Screening/ Randomization[b]	Treatment Visit[c]	Waiting Period	Telephone Contact	Telephone Contact	Assessment Visit[d]	Telephone Contact	Telephone Contact	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit	Follow-up Visit (EOS)	Unscheduled Visit[e]
Visit	1	2	n/a	TCM1	TCM2	3	TCM3	TCM4	4	5	6	7	8	9	10	n/a
Day/Week/Month	D-28 to D0	D1/W1	W2 to W13	M1	M2	M3	M4	M5	M6	M9	M12	M15	M18	M21	M24	n/a
Window	n/a	D0 +0/+28 d	n/a	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	±2 wks	n/a
CT Urogram, retrograde pyelogram or MRI[m]	X															
Cystoscopy (white light)	X					X			X	X	X	X	X	X	X	X
Voiding urine cytology (send to central pathology)[n]	X					X			X	X	X	X	X	X	X	X
Cold cup biopsy (send to central pathology)[o]	X															
Randomization	X															
Biopsy remaining lesions if indicated (send to central pathology)						X			X	X	X	X	X	X	X	X
Complete eCRFs	X	X				X			X	X	X	X	X	X	X	X
TURBT		X				X[p]										

Abbreviations: 3-M DAV = 3-Month disease assessment visit; AE = adverse event; CA = cancer; CT = computed tomography; d = day; D= Visit Day; eCRF =electronic case report form; EOS = end-of-study; FUP = Follow-up Period; ICF = informed consent form; LG = low grade; M = month; MRI = magnetic resonance imaging; n/a = not applicable; NCR = Non-complete response; SAE = serious adverse event; TCM = telephone contact month; TURBT = Transurethral Resection of Bladder Tumor; QLQ-NMIBC24 = Quality of Life Questionnaire for NMIBC; UGN-102 = UGN-102 (mitomycin) for intravesical solution; UTUC = upper tract urothelial carcinoma; W = Week: wks = weeks; WOCBP = women of child-bearing potential.

Notes: Primary disease assessment/response evaluation will be performed at the post 3-Month visits in the Follow-up Period.

a. For those patients in the follow-up period who have a disease recurrence or progression, the EOS Visit needs to be completed.
b. The screening period is up to 14 days for patients that do not need a screening biopsy and up to 28 days for patients that need a screening biopsy (see Section 8.1.1). Randomization 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. Screening procedures are to provide evidence of low grade NMIBC and no evidence of high grade disease.
c. Windows are provided to accommodate patient logistics in scheduling. Day 1 does not necessarily need to be the day after Day 0, e.g., in the event additional time is required to initiate treatment due to logistics such as scheduling procedure. Every effort should be made to minimize the time interval between diagnosis and treatment.
d. Patients who discontinue from the study before the 3-Month Visit should have all assessments specified for the EOS Visit as their EOS assessments.
e. If an unscheduled visit is required, assessments should be performed as appropriate to the needs of the visit, although safety assessments should be performed, if feasible.
f. For baseline score.

g. Any past therapy (e.g., medical or surgical interventions) related to urothelial cancer will be recorded during Screening.
h. Performed prior to cystoscopy at Screening. See Section 8.3.1 for details.
i. Dipstick on-site; culture and sensitivity added at screening if positive for infection (at local laboratory).
j. Urine or serum pregnancy test (at local laboratory).
k. Pregnancy test at assessment visit for NCR patients who will undergo TURBT.
l. 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 Month-6 visit (Visit 4). Subsequent to the Month-6 visit, all SAEs (regardless of causality) and non-serious AEs assessed as related to study treatments (UGN-102 or TURBT) or study procedures should be collected until the EOS Visit.
m. CT Urogram, retrograde pyelogram, or MRI (if other tests are contraindicated) to rule out UTUC (acceptable if performed within 6 months of initial Screening Visit) (results assessed locally).
n. No cytology needed if results from a prior cytology within 6 weeks of initial Screening Visit are available.
o. Cold cup biopsy to confirm LG tumor performed only if not already performed within 8 weeks of initial Screening Visit. This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of tumor is not to be performed.
p. NCR patients at the 3-Month Visit will receive another TURBT and enter the FUP. TURBT will be scheduled as soon as possible at Month 3 and every attempt should be made to perform TURBT within 1 month of this visit. **Note:** If the Investigator determines that a formal TURBT in the operating room is unnecessary following cystoscopy and biopsy of remaining lesions (e.g., residual disease can be addressed by in office biopsy and/or fulguration), such an alternative procedure is permitted based on the Investigator's medical judgment.

Abbreviations

ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AST	Aspartate aminotransferase
BCG	Bacille de Calmette et Guérin
CBC	Complete blood count
CCGs	CRF Completion Guidelines
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CIS	Carcinoma in situ
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRO	Contract Research Organization
CRR	Complete response rate
CT	Computerized tomography
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease-free survival
DOR	Duration of response
DRC	Data Review Committee
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End-of-Study
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HG	High grade
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health Related Quality of Life
HR	Hazard Ratio
IB	Investigator’s Brochure

ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFA	Instructions for Administration
IFP	Instructions for Pharmacy
IND	Investigational New Drug
IP	Investigational Product
IQR	Interquartile range
IR	Intermediate Risk
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LG	Low grade
LPLV	Last patient last visit
LUTS	Lower urinary tract symptoms
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect model for repeated measures
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NDD	No detectable disease
NI	Non-inferiority
NMIBC	Non-muscle invasive bladder cancer
NCR	Non-complete response
PCS	Potentially clinically significant
PI	Principal Investigator
PPS	Per Protocol Set
PQC	Product Quality Complaint
PRO	Patient reported outcome
PT	Preferred Term
PUNLMP	Papillary Urothelial Neoplasm of Low Malignant Potential
QLQ	Quality of Life Questionnaire
QLQ-NMIBC24	Quality of Life Questionnaire for NMIBC
QC	Quality control
QLTs	Quality tolerance limits
QoL	Quality-of-Life
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMP	Study Monitoring Plan

SoA	Schedule of Activities
SoC	Standard of care
SOP	Standard Operating Procedure
SRT	Safety Review Team.
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-emergent adverse event
TNM	Tumor-Node-Metastases
TTR	Time to recurrence
TURBT	Transurethral resection of bladder tumor
UADR	Unexpected Adverse Drug Reaction
UC	Urothelial carcinoma/cancer
UGN-102	UGN-102 (mitomycin) for intravesical solution
US	United States
USP	United States Pharmacopeia
UTI	Urinary tract infection
UTUC	Upper tract urothelial carcinoma
WHO	World Health Organization
WOCBP	Women of child-bearing potential

2. Introduction

Non-Muscle Invasive Bladder Cancer

Urothelial cancer (UC) of the bladder is the second most common genitourinary malignancy in the United States (US), with an estimated 81,400 new cases diagnosed and 18,000 deaths from the disease in 2020 (ACS, 2020). Non-muscle invasive bladder cancer (NMIBC) accounts for about 80% of all bladder cancers (Kirkali, 2005). Patients with NMIBC can be segmented into 3 staging groups: patients with Ta tumors (70%), patients with T1 tumors (20%), and patients with carcinoma in situ (CIS) or Tis tumors (10%). Of these patients, approximately 70% have a tumor that is classified as low grade (LG), and approximately 30% have a tumor that is classified as high grade (HG). Ta and CIS tumors are limited to the urothelial layer, and T1 is limited to the lamina propria.

The standard treatment of NMIBC is transurethral resection of bladder tumor (TURBT) (Pereira, 2019). TURBT is associated with the typical risks of surgery including injury to the bladder and postoperative bleeding. Recurrence rates following standard of care (SoC) management range from 31% to 78% with the risk of progression to muscle invasion approaching 50% in patients with HG cancer (Babjuk, 2019). Tumor recurrence following TURBT can be attributed primarily to incomplete initial resection and, at least hypothetically, to tumor cell reimplantation following surgery (Anastasiadis, 2012; Brausi, 2002; Miladi, 2003). The effectiveness of intravesical therapy is limited by urine production, which results in drug dilution and periodic bladder emptying, and which limits the agent's time on target (Audenet, 2013; Dalton, 1991; Wientjes, 1991).

Chemoablation represents an attractive alternative to surgical therapy. It could avoid the morbidity and expense of surgery and may offer a more rational therapeutic approach to UC, which is generally multifocal and refractory to focal ablative interventions. Preliminary evidence documents the ablative capabilities of aqueous Mitomycin C, which has been applied successfully to the primary management of small UCs (Colombo, 2001; Gontero 2004, Maffezzini, 2007; Racioppi, 2010).

UGN-102

UroGen has performed two Phase 2a open-label dose-escalation studies (Study BL002, BL004) and one Phase 2 open-label active-control study (Study BL003) which showed a favorable safety and efficacy profile for UGN-102 in patients with LG NMIBC. Based on this initial experience, UroGen also conducted a Phase 2b UGN-102 study (Study BL005) in the US and Israel to corroborate the prior data and to determine pharmacokinetic parameters. Results from this Phase 2b study showed a complete response rate (CRR) of 65% (41/63) at 3 months after the first instillation of UGN-102, of which 61% (25/41) remained free of disease at 12 months after the first instillation of UGN-102.

Results to date from clinical studies are supportive for the determination of the long-term safety and efficacy profile of UGN-102 in the LG NMIBC with intermediate risk (IR) indication under the overall clinical development strategy for UGN-102.

2.1. Study Rationale

Study BL006

This study is a global, randomized, controlled, open-label Phase 3 study to evaluate the long-term efficacy and safety of intravesical UGN-102 given once weekly for a total of 6 doses in the treatment of patients with Low Grade Intermediate Risk Non-Muscle Invasive Bladder Cancer (LG IR-NMIBC). This study seeks to establish the efficacy of UGN-102 as a primary chemoablative therapy in the treatment of LG IR-NMIBC. The study models the clinical practice of neoadjuvant therapy in the subset of patients who do not achieve a complete response (CR) after receiving UGN-102 (i.e., when assessed at 3 months); such patients in clinical practice would be treated with TURBT per SoC. In addition, the study designates TURBT alone patients as a comparison population for patients treated with UGN-102 (with or without TURBT).

The BL006 study is supported by the results of a Phase 2b study (Study BL005) in patients with LG IR NMIBC. The favorable benefit-risk profile of UGN-102 observed in this study, including high rates of complete response (CR) and durable complete response (DCR), primarily mild to moderate adverse events (AEs), no treatment-related serious adverse events (SAEs) or hospitalizations, low number of treatment discontinuations, no organ dysfunction, and no adverse impact on health-related quality of life (HRQoL), suggests that treatment with UGN-102 may obviate the need for surgery in some patients and result in fewer clinically significant adverse effects than TURBT.

Background

UGN-102 consists of mitomycin for solution (40 mg x 2) and sterile hydrogel (a proprietary thermally responsive gel, 60 mL) to produce UGN-102 for subsequent intravesical installation via a sterile catheter. Upon reconstitution, UGN-102 will be administered to patients at a concentration of 1.33 mg/mL (56 mL instillation volume for a total of 75 mg mitomycin per dose). The product is administered as a liquid and solidifies in the bladder to create a drug depot, which retains the mitomycin longer at the target site of administration. The advantage of delivering mitomycin to the urinary bladder using UGN-102 relies on preclinical and clinical literature documenting that concentration and dwell time correlate directly with the therapeutic efficacy of mitomycin when used to treat UC (Barlogie, 1980; Slee, 1986; Walker, 1986; Ozawa, 1988; Perry, 1992; Nozue, 1995; Sadeghi, 1998).

Mitomycin functions as a bifunctional or trifunctional alkylating agent. It is most sensitive in the late G1 and early S phases, but overall is considered cell cycle phase non-specific (Badalament, 1997). The cell killing induced by mitomycin, as well as by other topical chemotherapy drugs, is proportional to the duration of exposure and to concentration (Serreta, 2008; De Bruijn, 1992; Sadeghi, 1998; Barlogie, 1980; Nozue, 1995; Schmittgen, 1991; Ozawa, 1988; Walker, 1986; Slee, 1986; Giesbers, 1989).

UGN-102 Investigational Product

UGN-102 is provided by UroGen as a single dose carton containing 2 vials of 40 mg mitomycin for solution, and one 60 mL vial of sterile hydrogel. The proprietary hydrogel, allows for a sustained release of mitomycin at the target site of administration, resulting in prolonged exposure of the tumor cells to mitomycin, where it can exert a chemical ablative effect.

Ancillaries required for admixture and administration of UGN-102 are shipped to clinical sites in separate boxes.

Preclinical studies of UGN-102 performed by UroGen demonstrated limited systemic absorption of mitomycin. In a porcine model, all mitomycin plasma concentrations were found to be substantially below 400 ng/mL, which is the drug concentration associated with myelosuppression (Dalton, 1991). In clinical studies, systemic levels of mitomycin were low and well-tolerated within the range considered safe. Systemic toxicity following intravesical therapy is uncommon because of the limited absorption of mitomycin. Myelosuppression occurs in < 1% of patients (De Bruijn, 1992). Investigators have reported that extended dwell times appear safe in humans (De Bruijn, 1992).

For further details of the preclinical and clinical studies conducted with UGN-102, refer to the Investigator's Brochure (IB) for UGN-102.

2.2. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of UGN-102 may be found in the IB.

2.2.1. Risk Assessment

Cystitis and Lower Urinary Tract Symptoms (LUTS)

Cystitis and other lower urinary tract symptoms (LUTS) may develop. Urine tests, including urinalysis and urine culture where indicated, will be checked regularly during the study to exclude urinary infection. Any symptoms will be treated by the Investigator according to local practice.

All of the symptoms described above are all well known in relation to standard mitomycin instillations and are not specific to UGN-102.

Currently, the SoC for NMIBC is TURBT. This surgical procedure has its own potential risks such as bladder perforation resulting in mitomycin leak, bladder scarring, and decreased bladder capacity; urinary retention requiring catheterization; and the need for anesthesia.

Moreover, during TURBT, tumor cells are released into the bladder cavity and may be seeded in denuded areas of the bladder where the urothelium is surgically interrupted. This is one of the reasons for the high rate of tumor recurrence and the use of immediate post-TURBT chemotherapy (usually mitomycin instillations). The high recurrence rate of NMIBC indicates that the current SoC is far from optimal.

Toxicity Associated with Systemic Absorption/Local Irritation

Although literature review did not demonstrate any side effects associated with the systemic absorption when mitomycin was administered topically, bone marrow toxicity (thrombocytopenia and leukopenia) and bladder toxicity are considered possible risks for patients. The complete blood count (CBC) and renal and liver function tests will be checked regularly during the treatment period. In case of clinically significant abnormalities, the Investigator will continue to follow the abnormal parameter until resolution, stabilization, or otherwise managed.

Allergic Response to Mitomycin

Mitomycin bladder instillations have been shown to cause allergic reactions in various degrees of toxicity in treated patients. Toxicities were found to be manageable most of the time by treating the patients with antihistamine drugs prior to and after the treatment, and with systemic steroids as needed. Signs of an allergic response will be closely monitored during the study.

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 unless they are required by local and/or hospital regulations. Any additional local COVID-19 related procedures (e.g., 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 randomization or during study conduct.

2.2.2. Benefit Assessment

The potential advantages of instillation of mitomycin in hydrogel are as follows:

- Extended exposure of drug for up to 8 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 (mitomycin + sterile hydrogel) are expected to improve mitomycin treatment efficacy and provide an alternative mode of ablation for NMIBC, which may be simpler and potentially better tolerated than current treatment modalities.

2.2.3. Overall Benefit: Risk Conclusion

The potential benefits exceed the risks observed so far in the development program. Since the risks are similar to those observed with intravesical mitomycin alone, and the expected benefits are to improve mitomycin's therapeutic efficacy and to expand its use, the overall benefit:risk ratio at this stage supports continued development of UGN-102.

3. Objectives and Endpoints

OBJECTIVE	ENDPOINT
Primary	
To evaluate the efficacy of UGN-102 with or without TURBT versus TURBT alone with respect to disease-free survival (DFS) in patients with Low Grade Intermediate Risk Non-Muscle Invasive Bladder Cancer (LG IR-NMIBC).	Disease-free survival (DFS) is defined as the time from randomization until the earliest date of any of the following events: • Failure to be rendered free of local disease at the 3-Month assessment after the TURBT procedure. • Recurrence of low-grade disease after the 3-Month assessment (i.e., during the follow-up period). • Progression to high-grade disease. • Death due to any cause.
Secondary	
1. To evaluate the efficacy of UGN-102 with or without TURBT versus TURBT alone with respect to: a) Time to Recurrence (TTR) b) Complete Response Rate (CRR) at 3-Month disease assessment c) Duration of Response (DOR) d) Avoidance of surgery (TURBT) for treatment of LG IR-NMIBC 2. To evaluate the safety profile of UGN-102 with or without TURBT versus TURBT alone 3. To assess the effect of UGN-102 with or without TURBT versus TURBT alone on Patient Reported Outcomes (PROs) including disease related symptoms, functioning, and health-related quality of life (HRQoL) 4. To evaluate visit level Complete Response Rate (CRR)	1. The following efficacy endpoints will be evaluated: a) Time to recurrence (TTR) is defined as the time from randomization until the earliest date of recurrence of low-grade disease or progression to high-grade disease. b) Complete response rate (CRR), defined as the proportion of patients who achieved CR at the 3-Month disease assessment. c) Duration of response (DOR), defined as the time from first documented CR until the earliest date of any of the following events: • Recurrence of low-grade disease. • Progression to high-grade disease. • Death due to any cause. d) Proportion of patients requiring TURBT in each arm and average number of TURBT interventions per patient in each arm 2. The safety profile of UGN-102 and TURBT will be evaluated as assessed through standard clinical and laboratory tests (hematology and chemistry, urinalysis, physical examination, vital sign measurements, diagnostic tests, etc.) and through the collection of reports of adverse events (AEs) and serious adverse events (SAEs) including AEs of special interest. 3. Changes from baseline in HRQoL measures assessed by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire for Non-muscle Invasive Bladder Cancer patients (EORTC-QLQ-NMIBC24). 4. Observed CRR at scheduled disease assessment timepoints, defined as the proportion of patients who had CR at 3-Month disease assessment and maintained CR up to that particular follow-up disease assessment.

OBJECTIVE	ENDPOINT
Exploratory	
To explore potential differences in health resource utilization with UGN-102 vs TURBT in patients with LG NMIBC	Number of patients hospitalized for non-elective reasons, total number and length of non-elective hospitalizations

4. Study Design

4.1. Overall Design

This study is a global, randomized, controlled, open-label Phase 3 study designed to assess the long-term efficacy and safety of UGN-102 (mitomycin) for intravesical solution (i.e., intravesical instillation) with or without TURBT versus TURBT alone in the treatment of patients with LG IR-NMIBC defined as 1 or 2 of the following: multiple tumors, solitary tumor > 3 cm, or recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis at the initial Screening Visit) (Kamat, 2014). Eligible patients will be treated with 6 weekly instillations of UGN-102 followed by TURBT only if needed, or with TURBT alone.

Upon signing of informed consent patients will undergo a Screening Visit for eligibility evaluation. The screening period is 2 weeks if the patient's cold cup biopsy to confirm whether the LG tumor is historic (taken within 8 weeks of the Screening Visit) or 4 weeks if the patient's cold cup biopsy to confirm LG tumor is current (taken at the Screening Visit). Every effort should be made to minimize the time interval between diagnosis and treatment.

Eligible patients will be randomized in a 1:1 ratio to UGN-102 with or without TURBT or TURBT alone. Randomization will be stratified by the presence of previous LG NMIBC episodes within 1 year of the current diagnosis at the initial Screening Visit (yes versus no). Starting at Day 1, patients randomized to the UGN-102 group will receive 6 weekly intravesical instillations of UGN-102 followed by TURBT only if needed and patients randomized to the TURBT alone group will undergo TURBT followed by repeat TURBT if needed. The UGN-102 concentration to be used in this study will be 1.33 mg mitomycin per 1 mL. The volume of UGN-102 to be instilled will be 56 mL (75 mg of mitomycin).

Patients will enter a Waiting Period after receiving their last dose of study intervention in the Treatment Period. All patients (i.e., both treatment arms) will return to the clinic at approximately 3 months from the initiation of treatment (i.e., 7 weeks ±1 week after the last weekly instillation for the UGN-102 treatment arm; and 12 weeks ±1 week after TURBT for the TURBT alone treatment arm) for determination of response to ablative treatment. Following this initial evaluation, all patients confirmed to have had a CR will receive no further treatment and will enter the follow-up period of the study. Patients confirmed to have had a non-complete response (NCR) in either treatment arm will undergo TURBT of any remaining lesions and will then also enter the follow-up period of the study. **Note:** If the Investigator determines that a formal TURBT in the operating room is unnecessary following cystoscopy and biopsy of remaining lesions (e.g., residual disease can be addressed by in office biopsy and/or fulguration), such an alternative procedure is permitted based on the Investigator's medical judgment.

Response will be determined based on visual evaluation by cystoscopy (white light) (appearance, number, and size of any remaining lesions), histopathology of any remaining lesions, and voiding urine cytology. CR is defined as having no detectable disease (NDD) in the bladder and will be assessed visually via cystoscopy and by interpretation of urine cytology, and if indicated, biopsy results. Any lesions or suspect tissue must be biopsied to exclude recurrence.

During the follow-up period, patients will return to the clinic quarterly (e.g., at Months 6, 9, 12, 15, 18, 21, 24) until the end of their participation in the study to determine if they remain disease free. Patients determined to be disease free will remain on study until completion of all their

follow-up visits (approximately 24 months from the onset of treatment) or until disease recurrence, disease progression, or death is documented, whichever comes first. Patients determined to have had a protocol-defined recurrence or progression at any follow-up or unscheduled visit will be considered to have completed the study and released to the care (i.e., SoC) of their treating physician.

A patient will be considered to have completed the study if the patient completes all follow-up visits in accordance with the Schedule of Activities (SoA), has a recurrence or progression during the follow-up period, dies during the study, or is still in follow-up when End-of-Study (EOS) is declared.

Safety will be evaluated based on physical examination, laboratory assessments, and a review of AEs. 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 8.4.2.3.3), and qualified per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) as Grade 3 or 4 (Section 8.4.2.3.1 and Section 8.4.10).

4.2. Scientific Rationale for Study Design

The randomized, controlled, open-label design was chosen to confirm the results of Study BL005. Results from Study BL005 indicate that a dose regimen of 6 weekly instillations of UGN-102 (75 mg mitomycin) is effective and well tolerated in patients with LG NMIBC. Study BL005 which treated the LG IR-NMIBC population showed a CRR of 65% at 3 months after the first instillation of UGN-102 with 61% of CR patients remaining disease free at 12 months after the first instillation of UGN-102. The most commonly reported AEs (≥ 10% of patients) were dysuria, pollakiuria, hematuria, micturition urgency, urinary tract infection (UTI), and fatigue.

4.2.1. Patient Input into Design

Not applicable.

4.3. Justification for Dose

The UGN-102 dose of 75 mg was chosen based on both efficacy and tolerability. Study BL003 demonstrated numerically higher CRR for the 75 mg dose than for the 37.5 mg dose. In Study BL004, 120 mg of UGN-102 had a similar response rate to 75 mg and a higher rate of AEs (100% of patients in the 120 mg group); the 120 mg dose did not appear to have any added efficacy over 75 mg in the treatment of patients with NMIBC. Study BL005 showed a favorable efficacy and safety profile with 6 weekly instillations at 75 mg dose. Results showed a considerable treatment response with encouraging durability. The dose was considered well-tolerated and safe with 64% of patients showing study drug or procedure-related AEs.

For this randomized, controlled, open-label study (BL006), patients who do not achieve CR after 6 weekly instillations of UGN-102 75 mg will be treated with TURBT and then enter the follow-up phase of the study. In the event of recurrence in the follow-up phase, patients will exit the study to be treated according to SoC by their treating physician.

4.4. End-of-Study Definition

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

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.

4.5. Patient Completion and Withdrawal

A patient will be considered to have completed the study if the patient completes all follow-up visits in accordance with the SoA, has a recurrence or progression during the follow-up period, dies during the study, or is still in follow-up when EOS is declared.

A patient will be considered to have withdrawn from the study if the patient has not recurred, progressed, or died and is lost to follow-up, has withdrawn consent, is no longer being followed at the Investigator's discretion, or if the study is closed or terminated.

Refer further to details provided in Section 7.

5. Study Population

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

5.1. Inclusion Criteria

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

Informed Consent

1. Capable of giving signed informed consent as described in Section 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Age

2. Patient must be ≥ 18 years of age, at the time of signing the informed consent.

Type of Patient and Disease Characteristics

3. Patient who has newly diagnosed or historic LG NMIBC (Ta) histologically confirmed by cold cup biopsy at screening or within 8 weeks of screening;
4. Is at intermediate risk for progression, defined as having 1 or 2 of the following:
   a. presence of multiple tumors
   b. solitary tumor > 3 cm
   c. recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis at the initial Screening Visit)
5. Negative voiding cytology for HG disease within 6 weeks of screening;
6. 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) (Serum glutamic oxaloacetic transaminase [SGOT])/Alanine aminotransferase (ALT) (Serum glutamic pyruvic transaminase [SGPT]) ≤ 2.5 × ULN
   - Alkaline phosphatase (ALP) ≤ 2.5 × ULN
   - Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min
7. Has no evidence of active UTI.

Sex and Contraceptive/Barrier Requirements

8. 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 patient is the female partner of a male patient 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 (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectable, combined (estrogen/progesterone) oral contraceptives, intrauterine devices (IUDs-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 female 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:

Medical Conditions and Diagnostic Assessments

1. History of CIS on preliminary cystoscopy within 5 years of enrollment;
2. Received Bacille de Calmette et Guérin (BCG) treatment for UC within previous 1 year;
3. History of HG papillary UC in the past 2 years;
4. Known allergy or sensitivity to mitomycin that in the Investigator's opinion cannot be readily managed;
5. Clinically significant urethral stricture that would preclude passage of a urethral catheter;
6. History of pelvic radiotherapy;

7. History of:
    a. neurogenic bladder
    b. active urinary retention
    c. any other condition that would prohibit normal voiding
8. Past or current muscle invasive (i.e., T2, T3, T4) or metastatic UC or concurrent upper tract urothelial carcinoma (UTUC);
9. Current tumor grading of T1;

Compliance Assessment

10. 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;

Prior/Concomitant Therapy

11. History of prior treatment with an intravesical chemotherapeutic agent except for a single dose of chemotherapy immediately post any previous TURBT;

Prior/Concurrent Clinical Study Experience

12. Has previously participated in a study in which they received UGN-102;
13. Has participated in a study with an investigational agent or device within 30 days of randomization.

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 randomly assigned to study intervention. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE). Re-screening of patients is allowed in this study.

5.5. Strategies for Recruitment and Retention

The enrollment of this study has been stopped prematurely by the Sponsor in order to pursue an alternative development strategy for UGN-102 in the same patient population; 282 eligible patients who were screened on or before 10 Nov 2021 were randomized in this study. The study will be conducted primarily by appropriately trained urologists at approximately 120 investigative study sites in the United States, Israel, and Europe who provide care to patients with bladder cancer.

5.6. Criteria for Temporarily Delaying Administration of Study Intervention Administration

If at any time the Investigator identifies myelosuppression, evidence of active UTI, or other significant clinical event or laboratory derangements during the study outside the pre-defined parameters, treatment may be postponed for up to 4 weeks until clinical event resolves and/or laboratory values improve (See Section 8.3.3.1).

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(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 Intervention(s) 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 (see Table 1):

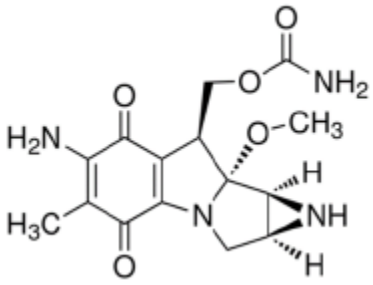
Table 1: UGN-102 Components

Component	Quantity (per single dose carton) †	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

Abbreviations: WFI = water for injection.
† For the proposed indication, each 40 mg mitomycin will be mixed with 3 mL sterile WFI 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-methoxymitosane
Formula: C15H18N4O5
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. Admixture and Administration Ancillary Supplies

All ancillary supplies used to prepare and administer the study treatment are detailed in the Instructions for Administration (IFA) and Instructions for Pharmacy (IFP).

6.1.3. Dosing and Administration

The patients entering this study will undergo 6 weekly instillations of UGN-102 if randomized to the UGN-102 treatment arm.

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

* Refer to UGN-102 Instructions for Administration (IFA) for detailed instillation instructions.

UGN-102 will be administered for therapy in the bladder as 6 weekly, consecutive instillations, at Study Visits 2a-2f (UGN-102 ± TURBT). Study treatment administration will be documented in the patient file, electronic Case Report Forms (eCRFs), and in the Drug Administration

Records. Patients randomized to the TURBT arm will undergo TURBT and will not receive UGN-102 during the study.

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 (Section 8.1.2). TURBT will be performed either as an ambulatory or an inpatient procedure according to the local standards of the study site.

6.1.4. Preparation and Administration Supplies

Preparation and administration supplies (or supplies manufactured for UroGen Pharma Ltd by a third party) provided for use in this study are:

Catalog number	Description	Manufacturer
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Other preparation and administration supplies (not manufactured by or for UroGen Pharma Ltd) provided for use in this study are:

Catalog number	Description	Manufacturer
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

6.2. Admixture/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. Prior to shipment of clinical supplies, the Sponsor or Sponsor's Designee should notify the Principal Investigator (PI) regarding the anticipated date of arrival at the hospital/clinic pharmacy. The investigational product (IP) will be sent to the site only after study approval by the Institutional Review Board (IRB) has been received. 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 CRA, 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 (i.e., batch records, Certificate of Analysis, etc.). 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 study 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 from the point the mixture is prepared until it is instilled, which includes the length of time at room temperature, as well as length of time at a refrigerated temperature.

6.2.5. Product Quality Complaint Handling

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging; i.e., 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 or storage at the pharmacy, 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 prior to drug dispensing.

If the PQC is combined 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 8.4.7 (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.

Product quality complaints 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: Randomization and Blinding

Patients will be assigned to one of the two treatment arms (Section 4.1) in a ratio of 1:1. Randomization will be stratified by the presence of previous LG NMIBC episodes within 1 year of the current diagnosis at the initial Screening Visit (yes versus no).

All patients will be centrally assigned to randomized study intervention using Interactive Response Technology (IRT). Before the study is initiated, the telephone number and call-in directions and/or the log in information and directions for the IRT will be provided to each site.

This is an open-label study; potential bias will be reduced by the central randomization. At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

1. Define two treatments to each patient and explain that the patient would receive one of the two treatments once randomized. This needs to be explained prior to randomization. The information will be recorded in the IRT system.
2. Obtain a unique randomization number via the IRT. The system will randomize the eligible patient to one of the two treatment arms. The stratification information of the patient must be obtained from the Investigator by the IRT prior to randomization.

If the patient is ineligible and not randomized, the IRT should be contacted to terminate the patient in the system. Once assigned, the randomization number must not be reused for any other patient and the randomization for that individual must not be changed, even if the patient is re-screened.

If a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

The treatment given to patients will be determined by the randomization scheme in the IRT. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list, using block randomization method will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment arm.

Although BL006 is an open-label study, access to treatment information by UroGen personnel will be restricted and will be by role basis to maintain the integrity of the study. An independent statistical group (external to Sponsor), not involved in the study conduct, will prepare data reports for the Data Review Committee (DRC) for this open-label study. Details will be presented in the DRC Charter and in the Trial Integrity Plan.

6.4. Study Intervention Compliance

The study treatment will be administered at specified treatment visits by properly trained study site staff members. Each drug administration (including date, time, volume administered) will be documented in the patient's file and eCRF.

6.5. Dose Modification

Not applicable.

6.5.1. Retreatment Criteria

Not applicable.

6.6. Continued Access to Study Intervention after the End of the Study

No study interventions will be administered to patients after the patient has exited from the study.

6.7. Treatment of Overdose

Not applicable.

6.8. Past/Concomitant and Prohibited Therapy

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 past therapy (e.g., medical or surgical interventions) related to urothelial cancer must be recorded in the eCRF along with:

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

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

Prohibited concomitant medications include:

- Systemic chemotherapy
- Intravesical chemotherapy
- Immunotherapy for bladder cancer treatment including but not limited to BCG.

NOTE: In patients undergoing protocol-specified TURBT, pre- or post-operative non-study chemotherapy is not permitted.

In cases of symptomatic UTI, the patient will be treated with a full 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 Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Rescue Medicine

Not applicable.

7. Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed 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.

Patients considered NCR in either study arm at the 3-Month Visit (Visit 3) will be treated with TURBT. **Note:** If the Investigator determines that a formal TURBT in the operating room is unnecessary following cystoscopy and biopsy of remaining lesions (e.g., residual disease can be addressed by in office biopsy and/or fulguration), such an alternative procedure is permitted based on the Investigator's medical judgment. Patients who are either CR or NCR at the 3-Month (Visit 3) in either study arm who have a recurrence of LG NMIBC or disease progression in the Follow-up Period will undergo EOS assessments at the EOS Visit and exit the study and will be treated according to best practice (i.e., SoC) by their treating physician.

If a patient discontinues study treatment during the treatment period or at any time prior to the 3-Month Visit, the patient, unless otherwise indicated, should remain in the study and all relevant visits and procedures should continue per protocol.

7.1.1. Temporary Withholding of Study Treatment

If at any time the Investigator identifies myelosuppression, evidence of active UTI, or other significant clinical event or laboratory derangements during the study defined by the parameters below, treatment may be postponed for up to 4 weeks until clinical event resolves and/or laboratory values improve (See Section 8.3.3.1):

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

7.1.2. Rechallenge

No change in dose will be performed for patients who re-initiate their study intervention after temporary withholding (See Section 7.1.1).

7.2. Patient Discontinuation/Withdrawal from the Study

A patient in this study 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 for safety, behavioral, or compliance reasons.

The Investigator may withdraw a patient from the study for the following reasons:

- Pregnancy
- Significant study non-compliance such that the Investigator believes that it is in the best interests of the study and/or the patient to withdraw the patient from the study
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient
- Patient is lost to follow-up (see Section 7.3)

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

At the time of discontinuing from the study, an EOS Visit should be conducted, as shown in the SoA. See SoA 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 intervention 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 study site staff.

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. 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 screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., 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.

8.1. Study Assessments and Procedures by Visit

8.1.1. Screening And Randomization Period (Day -28 to Day 0 or Day -14 to Day 0)

Note: For patients that need a biopsy, the screening period is up to 28 days. For patients that do not need a biopsy, the screening period is up to 14 days. Randomization 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. Screening procedures are to provide evidence of low grade NMIBC and no evidence of high grade disease.

8.1.1.1. Screening Visit (Day -28 to Day 0 or Day -14 to Day 0)

The following procedures will be performed at Screening (Visit 1):

All patients:

- Obtain written informed consent before any study-related procedures are performed
- Inclusion and exclusion criteria
- Demographics
- Administer QLQ-NMIBC24 questionnaire (for baseline score)
- Medical/Surgical and Smoking history
- Concomitant medication review
- Past therapy including any medical or surgical interventions related to urothelial cancer
- Full physical examination (including height and weight) and urology-oriented physical examination
- Vital signs (blood pressure, pulse rate, respiration rate, and body temperature)
- Clinical laboratory tests (serum chemistry and hematology) (at central laboratory)

- Urinalysis (dipstick on-site). If positive for infection, add culture and sensitivity at Screening (at local laboratory).
- Urine or serum pregnancy test (if appropriate) (at local laboratory)
- Cystoscopy and voiding urine cytology (at central pathology) (if not performed within 6 weeks of initial Screening Visit)
- Collection of a single representative cold cup biopsy, if no histologic confirmation of LG tumor within 8 weeks of initial Screening Visit (send to central pathology). *Note: This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of tumor is not to be performed.*
- Computerized tomography (CT) Urogram, retrograde pyelogram, or magnetic resonance imaging (MRI) (if other tests are contraindicated) to rule out UTUC (acceptable if performed within 6 months of initial Screening Visit)
- AE review

8.1.1.2. Randomization (Day 0)

The following procedures will be performed at Day 0:

All patients:

- Perform randomization
- Schedule TURBT or first UGN-102 instillation

8.1.2. Treatment Period: Visits 2a to 2f (Day 1 to 36 / Week 1 to 6) for UGN-102 ± TURBT Patients or Visit 2 (Day 1 / Week 1) for TURBT Alone Patients

Note: Windows are provided to accommodate patient logistics in scheduling. The window for Visit 2a (Day 1 / Week 1) for UGN-102 ± TURBT patients or Visit 2 (Day 1 / Week 1) for TURBT Alone patients is Day 0 +0/+28 days (i.e., within 28 days after randomization). Thus, Day 1 does not necessarily need to be the day after Day 0, e.g., in the event additional time is required to initiate treatment due to logistics such as scheduling procedure or training for UGN-102 instillation. Every effort should be made to minimize the time interval between diagnosis and treatment. The window for Visits 2b to 2f (Day 8 to 36 / Week 2 to 6) for UGN-102 ± TURBT patients is -1/+3 days. Instillations for UGN-102 ± TURBT patients should not occur more frequently than 6 days apart.

The following procedures will be performed at Visit 2 (Day 1) through Visit 2f (Day 36) for UGN-102 patients and at Visit 2 (Day 1) for TURBT Alone patients:

All patients:

- Administer QLQ-NMIBC24 questionnaire
- Concomitant medication review
- Urology-oriented physical examination
- Vital signs (blood pressure, pulse rate, respiration rate, and body temperature)

- Clinical laboratory tests (serum chemistry and hematology) (at central laboratory)
- Urinalysis (dipstick on-site)
- AE review

UGN-102 (± TURBT) patients:

- Administer study treatment*
- Keep patient in clinic for 30 to 60 minutes post instillation
- Urine or serum pregnancy test (At Visit 2a only) (if appropriate) (at local laboratory)

TURBT Alone patients:

- Perform TURBT
- Urine or serum or pregnancy test (At Visit 2 only) (if appropriate) (at local laboratory)

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

8.1.3. Waiting Period: Week 7 to 13 (UGN-102 ± TURBT) or Week 2 to 13 (TURBT Alone)

Patients will enter a Waiting Period after receiving their last dose of study intervention in the Treatment Period. The Waiting Period will extend up to the Visit 3 Disease Assessment Visit (i.e., for assessment of response) (Visit 3, Month 3).

8.1.4. Monthly Telephone Contact Visits: Months 2, 4, and 5 ± 1 week (UGN-102 ± TURBT) or Months 1, 2, 4, and 5 ± 1 week (TURBT Alone)

Patients will be contacted by phone at Month 1 (TURBT Alone patients) and Months 2, 4, 5 (all patients) in the first year Follow-up Period to check for the following:

- Concomitant medication review
- AE review

8.1.5. Disease Assessment Visit: Visit 3 (Month 3 ± 1 week)

The following procedures will be performed at Visit 3 (Month 3) (for determination of response to treatment):

All patients:

- Administer QLQ-NMIBC24 questionnaire
- Concomitant medication review
- Body weight
- Vital signs (blood pressure, pulse rate, respiration rate, and body temperature)

- Clinical laboratory tests (serum chemistry and hematology) (at central laboratory)
- Urinalysis (dipstick on-site)
- Cystoscopy and voiding urine cytology (at central pathology) for evaluation of durability response (Sections 8.2.1 and 8.2.2)
- Biopsy remaining lesions (if indicated; Sections 8.2.1 and 8.2.2) (send to central pathology)
- AE review

The following assessments apply only to NCR patients at Visit 3 (Month 3).

- Urine or serum pregnancy test (if appropriate) (at local laboratory)
- Schedule TURBT as soon as possible (Every attempt should be made to perform TURBT within 1 month of this visit)
- Perform TURBT (**Note:** If the Investigator determines that a formal TURBT in the operating room is unnecessary following cystoscopy and biopsy of remaining lesions (e.g., residual disease can be addressed by in office biopsy and/or fulguration), such an alternative procedure is permitted based on the Investigator's medical judgment.)

8.1.6. Follow-up Period including EOS Visit: Visit 4, 5, 6, 7, 8, 9, 10 (Months 6, 9, 12, 15, 18, 21, 24 (EOS) ± 2 weeks)

Follow-up visits start at Month 6 and continue every 3 months thereafter until completion of all the patient's follow-up visits at the EOS Visit (Visit 10, Month 24) or until recurrence/progression/death is documented, whichever comes first.

Note: *For those patients in the follow-up period who have a disease recurrence or progression, the EOS Visit needs to be completed.*

The following procedures will be performed at Follow-Up Visits including the EOS Visit (Visit 10, Month 24):

All patients:

- Administer QLQ-NMIBC24 questionnaire
- Concomitant medication review
- Vital signs (blood pressure, pulse rate, respiration rate, and body temperature)
- Clinical laboratory tests (serum chemistry and hematology) (at central laboratory) (at Visit 4, Month 6 only)
- Urinalysis (dipstick on-site)
- Cystoscopy and voiding urine cytology (at central pathology) for evaluation of durability response (see Section 8.2.4)

- Biopsy of remaining lesions (if indicated; Sections 8.2.1 and 8.2.2) (send to central pathology)
- AE review

8.1.7. Unscheduled Visits

When required, based on patient needs relating to the study or due to unforeseen circumstances, unscheduled visits can occur outside the scheduled window. The following procedures are recommended during these unscheduled visits, subject to the Investigator's judgment:

The following procedures will be performed at Unscheduled Visits:

All patients:

- Administer QLQ-NMIBC24 questionnaire
- Concomitant medication review
- Vital signs (blood pressure, pulse rate, respiration rate, and body temperature)
- Urinalysis (dipstick on-site)
- Cystoscopy and voiding urine cytology (at central pathology) for evaluation of durability response (see Section 8.2.4)
- Biopsy of remaining lesions (if indicated; Sections 8.2.1 and 8.2.2) (send to central pathology)
- AE review

8.2. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3 and Section 1.4).

8.2.1. 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 (NCR or suspected tissue)
- Voiding urine cytology by central pathology lab

8.2.2. Evaluation of Response at 3-Month Visit and Follow-up Visits (Disease Assessment)

Patient response will be determined at the 3-month Visit and every 3 months thereafter 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:
  1. If visual assessment indicates no remaining tumors and urine cytology is not consistent with presence of UC, the patient has NDD and CR.
  2. 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:
  1. 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 that 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**: Recurrence will be assessed every 3 months at Follow-up Visits 4, 5, 6, 7, 8, 9, and 10 (until the end of participation in the study defined as until completion of all follow-up visits or until recurrence/progression/death is documented) for all patients. 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 (TNM) classification and graded according to the 2004 World Health Organization (WHO) classification of tumors. Any noted progression of tumor in terms of transition to high grade (central lab), muscle invasion (central lab), or distant disease (local assessment) will be documented by the site in the eCRF, and the patient will be considered to have completed the study at that time (see Section 8.2.3).
- 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.
  1. 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.
  2. 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).

3. 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. Please note that a decision for the need of TURBT must be made at the 3-month Visit assessment. In case the evaluation of response is 'indeterminate' at this visit, sites must perform the required procedures as soon as possible in order to have an adequate response evaluation.

8.2.3. Assessment of Tumor Progression

The overall risk of progression for patients with LG papillary NMIBC at intermediate risk of recurrence ranges from 1 to 5% at 1 and 5 years (Babjuk, 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. The patient will be considered to have completed the study at that time and will be treated according to best practice (i.e., SoC) by their treating physician.

8.2.4. Assessment of Tumor Recurrence

Follow-up will be conducted in patients who were defined as having CR or NCR (after undergoing TURBT) at the 3 Month Visit.

Starting with the first follow-up visit (Study Visit 4, Month 6) and continuing at Visits 5, 6, 7, 8, 9, and 10 (Months 9, 12, 15, 18, 21, and 24, respectively), information regarding disease status based on cystoscopy, cytology, and biopsy (when applicable) should be recorded. If a patient is defined as having recurrence, complete documentation should be obtained. If a patient has a positive urine cytology and/or a positive biopsy for cancer, they are considered as having urothelial cell cancer recurrence. If urine cytology is consistent with LG NMIBC but the biopsy is negative, the patient should be evaluated for the presence of UTUC. If the patient is positive for UTUC that was not present at baseline and there is no evidence of tumor within the bladder, this is considered new disease and the patient remains a CR for their LG NMIBC. If the patient is negative for UTUC, the urine cytology should be repeated. If the repeat urine cytology is consistent with urothelial cancer, the patient should be classified as recurrence.

8.2.5. Pathological Evaluation

Biopsies and urine cytology specimens obtained at screening or any other visit should be evaluated by the central laboratory (pathologist). Pathology reports from the central laboratory will be provided to Investigators.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1. Physical Examinations

At the visits specified in Section 1.2 and Section 1.3, a full physical examination or urology-oriented physical examination will be performed. The patient's physical condition will be examined and documented. This includes examination of main body systems, with focus on the urinary system. The examinations to be performed are summarized in Table 3.

Table 3: Physical Examinations

General Physical Examination will be performed at Screening Visit 1 (both treatment arms)	**Urology-Oriented Physical Examination will be performed Screening Visit 1* and the Treatment Period (Study Visits 2a-2f for UGN-102 ± TURBT or Visit 2 for TURBT Alone) (both treatment arms)**
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 Rectal examination (for male and female patients) (Screening visit only) Bimanual examination (female patients – Screening visit only)

* Performed prior to cystoscopy at Screening.

8.3.2. Vital Signs

At each visit, the following vital signs measurements are to be taken:

- Temperature, pulse rate, respiratory rate, and 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.

8.3.3. Clinical Safety Laboratory Assessments

Samples for hematology and serum chemistry assessments will be taken according to the SoA in Section 1.3 and Section 1.4 and tested at the central laboratory. The assessments to be performed are listed in Table 4. Additional tests may be part of a clinical site's local laboratory's standard panel and therefore reported along with these specified tests.

8.3.3.1. Other significant laboratory derangements

If at any time the Investigator identifies myelosuppression, evidence of active UTI, or other significant clinical event or laboratory derangements during the study defined by the parameters below, treatment may be postponed for up to 4 weeks until 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 (SGOT)/ALT (SGPT) ≥ 5 × upper limit of normal (ULN)
- Lab evidence of active UTI

The following table describes laboratory assessments to be performed in this study (Table 4):

Table 4: Laboratory Safety Assessments*

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

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; EDC = electronic data capture; eGFR = estimated glomerular filtration rate; GGT = gamma-glutamyltransferase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
* Laboratory samples will be kept per storage requirements as stated in the lab manual until shipped to central laboratory for analysis.

Refer to the SoA (Section 1.3 and Section 1.4) for the timing and frequency of clinical laboratory tests.

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 (e.g., in case of either temporary discontinuation) or within 4 weeks after the last administered dose of study intervention (i.e., 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.

All protocol-required laboratory tests, as defined in Table 4, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3 and Section 1.4).

A central laboratory will be used in this study, except for the pregnancy test (either urine or serum) and urinalysis which are performed at site or locally. 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 (e.g., AE), then the results must be recorded.

8.3.4. Urinalysis

At the visits specified in Section 1.3 and Section 1.4, samples will be taken for urinalysis, including culture and sensitivity (if indicative of infection) at the Screening Visit, and when otherwise clinically indicated.

8.3.5. Pregnancy Testing

A urine or serum pregnancy test will be conducted in female patients of childbearing potential at the Screening Visit, Visit 1, and Visit 2a (UGN-102 ± TURBT Patients) or Visit 2 (TURBT alone patients). A urine or serum pregnancy test is also performed at Visit 3 for NCR patients in both treatment arms. 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 prior to study treatment administration.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 8.4.2. All AEs and SAEs will be collected from the signing of the ICF (Section 8.4.3).

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 Section 8.4.3 and remain responsible for following up all applicable AEs including those that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study treatment or from participation in the study (see 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 8.4.2, Section 8.4.6, and Section 8.4.7.

8.4.1. Safety and Other Assessments

8.4.1.1. Safety Assessment Overview

The safety of the 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 (PCS)
- Clinically meaningful changes in physical examination findings including vital signs

8.4.1.2. Quality of Life Assessment EORTC QLQ – NMIBC24

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for NMIBC (QLQ-NMIBC24) is a 24-item validated, evidence-driven survey that assesses Health Related Quality of Life (HRQoL) for patients with intermediate to high risk NMIBC. It is designed to be administered at Visit 1, Visit 2a-2f (UGN-102 ± TURBT) or Visit 2 (TURBT Alone), at 3, 6, 9, 12, 15, 18, 21, and 24-monthly intervals, and at Unscheduled Visits. The NMIBC24 is the only instrument exclusively designed to compare HRQoL between non-muscle-invasive treatment modalities. Refer to Appendix 2.

8.4.2. Adverse Events and Serious Adverse Events

8.4.2.1. Definition of Adverse Events

An AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 Code of Federal Regulations [CFR] 312.32 [a]; European Directive 2001/20/EC). 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, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., 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 intervention 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 intervention 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 (e.g., 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.

8.4.2.2. Definition of Serious Adverse Events

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 (e.g., 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.

8.4.2.3. Classification of an Adverse Event

8.4.2.3.1. Severity of Event

The severity (intensity) of an AE is to be graded by the Investigator according to CTCAE version 5.0 (CTCAE, 2017). General rules are as follows:

1 **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

2 **Moderate:** minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL)

3 **Severe** or **medically significant** but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

4 **Life-threatening consequences:** urgent intervention indicated (SAE)

5 **Death related to AE** (SAE)

8.4.2.3.2. 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 intervention 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 make 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.

8.4.2.3.3. 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 (UADR) 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 UADR that at any dose also meets the criteria for SAE.

8.4.3. 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 Month-6 visit (Visit 4). Subsequent to the Month-6 visit, all SAEs (regardless of causality) and non-serious AEs assessed as related to

study treatments (UGN-102 or TURBT) or study procedures should be collected until the EOS Visit at the time points specified in the SoA (Section 1.3 and Section 1.4). Information will be captured on the appropriate eCRF including event description, time of onset, clinician's assessment of severity, relationship to study treatment and study procedure (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All collected reportable AEs occurring while on study must be documented appropriately. All collected AEs will be followed to adequate resolution/stabilization.

If the study patient's condition deteriorates at any time during the study, it will be recorded as an AE. AEs reported from the time of study treatment administration will be considered as treatment-emergent adverse events (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 phone calls per the SoA (Section 1.3 and Section 1.4), the Investigator should inquire about the occurrence of AE/SAEs since the last visit/phone call. 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 intervention or study participation, the Investigator must promptly notify the Sponsor within 24 hours.

8.4.4. 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.

8.4.5. Follow-up of AEs and SAEs

After the initial collected AE/SAE report, the Investigator 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 8.4.7.

8.4.6. 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 intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/Independent Ethics Committee (IEC), and Investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., 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.

8.4.7. Serious Adverse Event Reporting

The Investigator will immediately report to the Sponsor any SAE, whether or not considered study treatment-or study procedure related, 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 (IND) 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.

8.4.7.1. 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 electronic data collection 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]

Study Medical Monitor
[redacted], MD, UroGen Pharma
[redacted]

8.4.8. Pregnancy

For any female patient who becomes pregnant while participating in the study, the Investigator shall immediately discontinue study treatment and ensure expedited reporting of the event within 24 hours (see Section 8.4.6). The pregnancy will be followed to term and the outcome reported.

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

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.

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.6. 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.

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

Not applicable.

8.4.10. Adverse Events of Special Interest

In this study, AESIs will be reviewed by the Sponsor on an ongoing basis. There are no requirements for the Investigator to make determination of AESIs and Investigators are to report AEs (including AESIs) in a consistent manner as described in Section 8.4.3.The list of AESIs is based on the most current safety profile of UGN-102 within the overall clinical development program.

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
- LUTS (CTCAE Grade 3 or 4)

8.5. Pharmacokinetics

Pharmacokinetic and pharmacodynamic parameters are not evaluated in this study.

8.6. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics/Medical Resource Utilization and Health Economics

The following health economics or medical resource utilization and health economics parameters may be exploratively summarized in this study (at analysis level):

- Number of patients hospitalized for non-elective reasons, total number and length of non-elective hospitalizations

9. Statistical 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. All time-to-event variables (e.g., DFS, DOR, TTR) will be analyzed using Kaplan-Meier method.

9.1. Statistical Hypotheses

UroGen Pharma Ltd. (Sponsor) closed enrollment in Study BL006 on 10 Nov 2021 in order to pursue an alternative development strategy for UGN-102 in patients with LG IR NMIBC. Although patients who are already randomized are permitted to continue their study participation until the EOS, the study is not powered to perform any hypothesis testing. Therefore, all analyses will be descriptive in nature.

9.2. Sample Size Determination

The enrollment of this study has been stopped prematurely by the Sponsor in order to pursue an alternative development strategy for UGN-102 in the same patient population; 282 eligible patients who were screened on or before 10 Nov 2021 were randomized in this study.

9.3. Analysis Sets

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

Analysis Set	Description
Intent-to-Treat (ITT)	The Intent-to-Treat (ITT) set includes all randomized patients who received any dose of UGN-102 (treatment arm) or at least one TURBT intervention (control arm). According to the ITT principle, patients will be analyzed according to the treatment and strata they have been assigned during randomization. The ITT will be the primary population for all efficacy analysis.
Full Analysis Set (FAS)	The Full Analysis Set (FAS) comprises all randomized patients. Patients will be analyzed according to the treatment and strata they have been assigned to during the randomization procedure. Sensitivity analyses of the efficacy endpoints may be performed using data from FAS if the FAS and ITT differ.
Safety Set	The Safety Set includes all patients who received any dose of UGN-102 (treatment arm) or at least one TURBT intervention (control arm). Patients will be analyzed according to the study treatment they actually received. All safety analyses will be conducted using the safety population.
Per Protocol Set (PPS)	The Per Protocol set (PPS) will include the subset of the patients in the ITT without major protocol deviations that would confound efficacy evaluation. All protocol deviations or conditions leading to exclusion from the PPS will be detailed in the protocol deviation plan and SAP. Sensitivity analyses of the primary endpoint of DFS may be performed using data from PPS if the PPS and ITT differ sufficiently.

As described in Section 4.1, patients considered NCR at the 3-Month Visit may receive an alternative procedure (e.g., biopsy and/or fulguration) if a formal TURBT is unnecessary based on the Investigator's medical judgment. All NCR patients at the 3-Month Visit, irrespective of their mode of treatment, will be included in the analysis.

9.4. Statistical Analyses

The SAP will include a more detailed description of the statistical analyses described in this section.

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% confidence interval (CI) for proportions using the exact approach. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation (SD), coefficient of variation (if appropriate), median, minimum and maximum, percentiles, and 95% CI for means of variables.

Multiplicity

Since no formal hypothesis will be tested, there will be no adjustment for multiplicity. All endpoints will be analyzed and interpreted descriptively.

9.4.2. Primary Endpoint(s)

The primary efficacy endpoint DFS is defined as the time from randomization until the earliest date of failure to be rendered free of local disease at the 3-Month assessment after the TURBT procedure, recurrence of low-grade disease after the 3-Month assessment (i.e., during the follow-up period), progression to high-grade disease, or death due to any cause.

NCR at the 3-Month disease assessment in the UGN-102 ± TURBT treatment arm is not considered as a DFS event because treatment failure is not an event in a neoadjuvant setting. However, NCR (i.e., residual disease) at the 3-month disease assessment after the TURBT procedure (i.e., in the TURBT arm) will be considered as a DFS event. Progression to HG disease any time during the study (even at the 3-month disease assessment) will be considered as a DFS event in either arm.

DFS will be analyzed based on the data observed in the ITT population, according to the treatment arm patients were randomized and the strata they were assigned at randomization. The distribution of DFS will be estimated using the Kaplan-Meier method. The median DFS along with 95% CIs will be presented by treatment arm.

A stratified Cox regression model will be used to estimate the HR of DFS, along with 95% CIs (using the same strata information as above). No p-value will be generated.

The ITT set that includes all randomized patients who received any dose of UGN-102 (treatment arm) or at least one TURBT intervention (control arm), will serve as the primary population for the analyses of efficacy data in this study.

Handling of Missing Values/Censoring/Discontinuations

If a patient has not had an event, DFS will be censored at the date of the last adequate disease assessment (i.e., a visit when all scheduled disease assessments have been done).

DFS will be censored if no DFS 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.

Supportive Analyses

The primary analysis for DFS may be repeated with data based on FAS and PPS if the FAS/PPS and ITT differ sufficiently.

Subgroup Analysis

Subgroup analyses will be performed on each level of the following factors using ITT population.

Subgroups will include (but not limited to):

- Age group (<65, 65 to <75, ≥75 years),
- BMI category (<30 kg/m^2, ≥30 kg/m^2),
- Sex (male, female)
- Tumor size (>3 cm, ≤3 cm)
- Tumor (single, multiple)
- Recurrence within 1 year of current diagnosis (0 vs ≥1).

9.4.3. Secondary Endpoint(s)

The secondary efficacy endpoints are described below. All analyses will be evaluated in ITT set without formal comparison. Sensitivity analyses may be performed using data from FAS if the FAS and ITT differ.

Time to recurrence (TTR)

Time to recurrence (TTR) is defined as the time from randomization until the earliest date of recurrence of low-grade disease or progression to high-grade disease. The distribution function of TTR will be estimated using the Kaplan-Meier method. The median TTR along with 95% CIs will be presented by treatment arm.

Complete Response Rate (CRR) at 3-Month Disease Assessment

Complete response rate (CRR), defined as the proportion of patients who achieved CR at the 3-Month disease assessment. The responses at 3-Month will test the CRR defined as percentage of patients with CR at the 3-Month visit. CRR will be presented by treatment arm along with approximate 95% CIs.

Duration of Response (DOR)

Duration of response (DOR), defined as the time from first documented CR until the earliest date of recurrence of low-grade disease, progression to high-grade disease, or death due to any cause. DOR applies only to patients who achieved CR at the 3-Month disease assessment. The

distribution function of DOR will be estimated using the Kaplan-Meier method. The median DOR along with 95% CIs will be presented by treatment arm.

Observed CRR at Scheduled Disease Assessment Timepoint

Observed CRR at scheduled disease assessment timepoints, defined as the proportion of patients who had CR at the 3-Month disease assessment and maintained CR up to that particular follow-up disease assessment. CRR will be presented with nominal 95% exact CI (Clopper-Pearson) for each treatment arm at each scheduled timepoint.

Incidence of TURBT

Proportion of patients requiring TURBT in each arm and average number of TURBT intervention per patient in each arm will be summarized.

Changes from Baseline in HRQoL

The EORTC QLQ-NMIBC24 questionnaire will be used to assess patients' satisfaction with their treatment. The EORTC QLQ-NMIBC24 is a self-reported 24-item NMIBC specific instrument that assesses 11 domains: 2 functional scales or single item (sexual function, sexual enjoyment), and 9 symptom scales or single items (urinary symptoms, malaise, future worries, bloating and flatulence, male sexual problems, intravesical treatment issues, sexual intimacy, risk of contaminating partner, and female sexual problems).

A mixed effect model for repeated measures (MMRM) will be performed to evaluate the two treatment arms with respect to changes in the QLQ-NMIBC24 measures. Scoring of raw Quality of Life (QoL) and methods for handling of missing items or missing assessments will be handled according to the scoring manual. No imputation will be applied if the total or subscale scores are missing at a visit, since all available data during the study will be used in the MMRM analysis which assume that the missing scores at any time point are missing-at-random. Additional sensitivity analysis may be performed to assess the possible violation of missing-at-random assumption for the missing data mechanism if deemed appropriate. Details will be specified in the SAP.

Descriptive statistics will be used to summarize the scored scales at each scheduled assessment time point for each of the domains. 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 during the treatment period will be included in the change from baseline analyses.

No formal statistical test will be performed and hence no multiplicity adjustment will be applied. The ITT will be used for analyzing QoL data.

9.4.4. Exploratory Endpoints

Number of patients hospitalized for non-elective reasons, total number and length of non-elective hospitalizations will be explored and summarized by treatment arm in this study. Additional exploratory endpoints may be added in the SAP.

9.4.5. Safety Analysis

Safety analyses will be conducted for the safety set. The assessment of safety will be based mainly on the frequency of AEs and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., physical examination, vital signs) will be considered as appropriate. All listings and tables will be presented by treatment arm.

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

1. Pre-treatment period: from day of patient's informed consent to the day before administration of first treatment
2. On-treatment period: from day of first treatment administration to **30** days after last treatment administration
3. Post-treatment period: starting at day 31 after last treatment.

Adverse Events and Serious Adverse Events

Summary tables for AEs will include only AEs that started or worsened during the study (i.e., on-treatment and post-treatment periods), the TEAEs. However, all safety data will be listed and those collected during the pre-treatment and post-treatment period are to be 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 by treatment arm.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of adverse event and treatment arm.

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 adverse events of interest may be based on the Safety Review Team (SRT) agreements in place at the time of reporting. The SRT agreements are based on a review of the MedDRA dictionary.

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

Clinical Laboratory Tests

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 (e.g., 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 by-treatment 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

Full physical examination will be performed at screening only. Urology oriented physical examination will be performed at screening and during treatment visits. Details are provided in Section 1.3, Section 1.4 and Section 8.3.1. Any clinically relevant changes of urological physical examination will be recorded on the AE Sections of the eCRF and reported with AEs as described above.

Vital Signs

The following analysis will be performed for vital signs:

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

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

9.4.6. Other Analysis

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

9.5. Interim Analysis

No interim analysis is planned for this study. Final analysis will be performed after all patients have completed the study.

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 (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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 prior to 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 serious adverse events (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 Code of Federal Regulations (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. Finance and Insurance

10.1.2.1. Finance

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

10.1.2.2. Insurance

The study will be covered in accordance with local requirements and per the clinical trial agreement (CTA).

10.1.3. 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 prior to 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, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

10.1.3.1. Consent Procedures and Documentation

Informed consent is a process that is initiated prior to 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 prior to signing. The patients should have the opportunity to discuss the study with their family or surrogates or think about it prior to 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. Patients or their legally authorized representative defined as per the applicable country-specific regulations will be required to sign a statement of informed consent prior to 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 rescreened are required to sign a new ICF.

10.1.4. 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 which 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 clinical study 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 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, or Sponsor requirements.

10.1.5. Data Review Committee

Since there is no interim analysis planned for this study, there will be no external data review committee (DRC).

10.1.6. 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.

10.1.7. 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.

10.1.8. 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 a study site visit log that will be kept at the site. Remote 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 electronic case report form (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 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.

10.1.9. Data Quality Assurance

All patient data relating to the study will be recorded on electronic or paper CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of eCRFs will be provided in the CRF Completion Guidelines (CCGs).

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 (i.e., data QC checks) will be implemented for the electronic data capture (EDC). Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

Monitoring details describing strategy methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

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

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 (e.g., 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.

10.1.10. Data Handling and Record Keeping

10.1.10.1. 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 electronic data capture 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.

10.1.10.2. 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.

10.1.11. 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 principal investigator (PI)/study staff is responsible for knowing and adhering to their IRB/IEC requirements.

10.1.12. 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.

10.1.13. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

Study/Site Termination

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

The Investigator may initiate study-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 a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention 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 participants by the Investigator
- Total number of participants 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 Food and Drug Administration (FDA).

10.1.14. 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.

10.1.15. 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.

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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 thereafter (i.e., months 6, 9, 12 etc.).

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. Please note that a decision of the need for TURBT must be made at the 3-month visit assessment. In case the evaluation of response is 'indeterminate' at this 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 7 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).

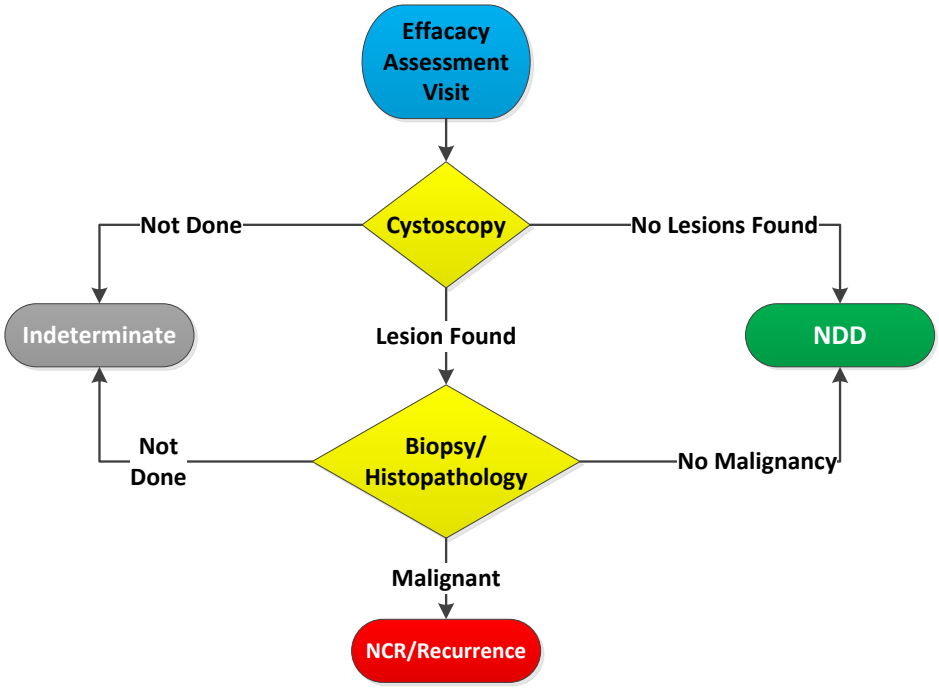
c) If cystoscopy was not performed and/or the biopsy was not done when indicated, the evaluation will be indeterminate.

Table 5: 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 of the Bladder (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.

1. If there are no visible lesions on cystoscopy, or a biopsy reveals no evidence of LG NMIBC, the urine cytology must be repeated.
2. If the repeat cytology result is either 1, 2, or 3, then NDD is determined by cytology.

3. 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.
    i. If UTUC is diagnosed, then NDD is determined by cytology.
    ii. 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).
        1. If the histopathology of any of these biopsies reveals malignancy, patient's response will be recorded as NCR/recurrence.
        2. 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 6: Evaluation Based on Urine Cytology, Diagnosis of UTUC and Random Bladder Biopsies

Cytology Results	Repeat Cytology Required? *	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 **	Will be determined by the results of the biopsies. ***
Not done	-	-	-	-	Indeterminate

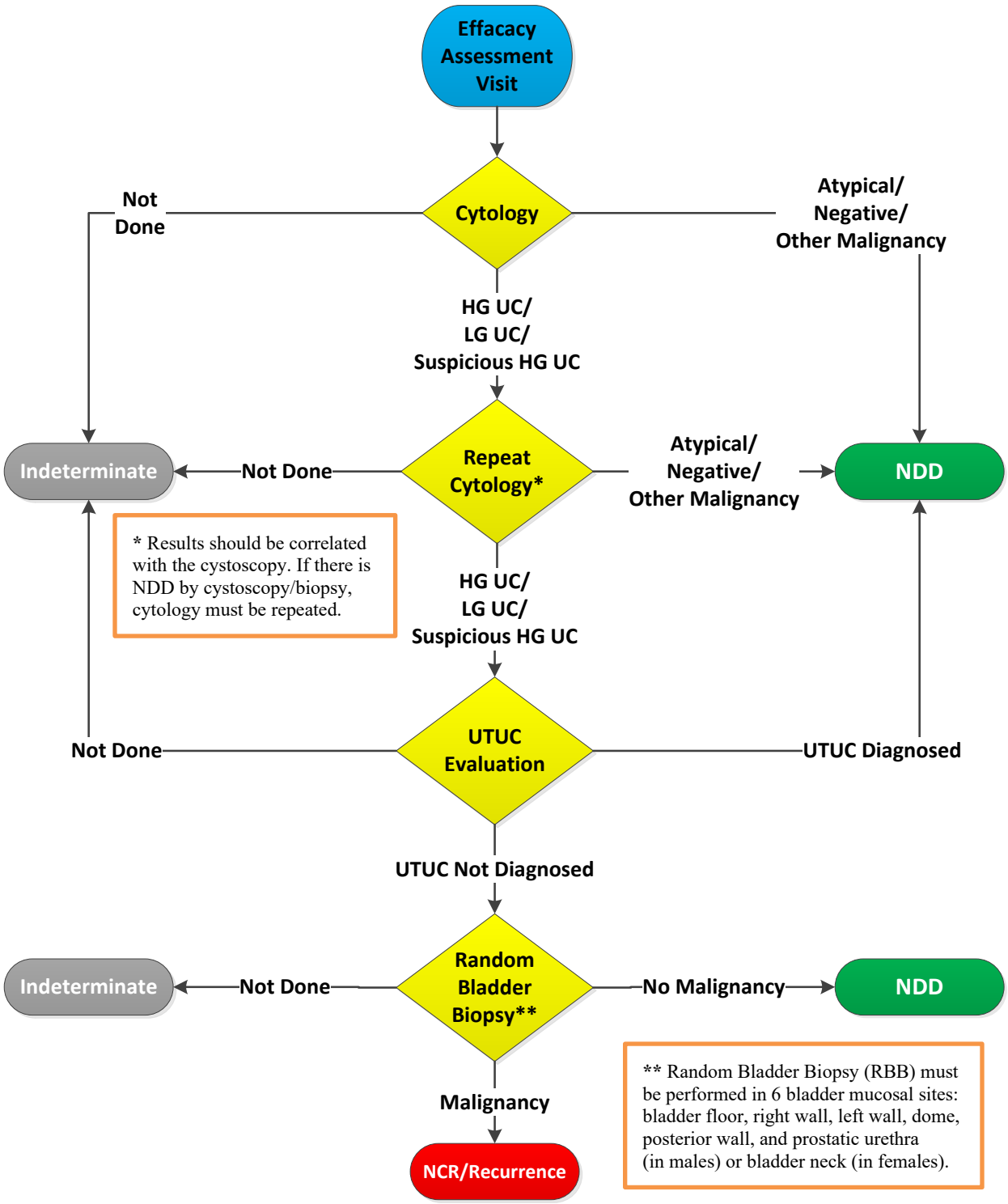
HG = high grade; LG = low grade; NA = not applicable; NCR = non-complete response;
NDD = no detectable disease; UC = urothelial carcinoma; UTUC = upper tract urothelial carcinoma.

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

** A Random Bladder Biopsy (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).

*** 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 Biopsy



3. Overall Response based on Cystoscopy, Biopsy/Histopathology, Cytology and 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 7: 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*	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.
* These scenarios will be adjudicated on a case-by-case basis.

Appendix 2. EORTC QLQ – NMIBC24

Please go on to the next page

Appendix 3. Protocol Revision History

Version	Date	Description of Changes	Brief Rationale
1.1	16 Sep 2020	• Removed Sponsor signature page • Revised the visit window for Visit 2a (UGN-102 patients) and Visit 2 (TURBT patients) in Sections 1.3, 1.4, and 8.1.2 • Edited title and content of Sections 6.1.2 and 6.1.4 • Corrected visit number in Section 8.1.5 • Deleted sentence in Section 8.4.3	[redacted]
2.0	20 Dec 2021	• Updated key roles and contact information • Added notification of early study enrollment closure • Clarified that NCR patients at the 3-month Visit may undergo an alternative procedure (e.g., biopsy and/or fulguration) to address residual disease if a formal TURBT is unnecessary based on the Investigator's medical judgment • Revised statistical considerations to reflect that the study is not powered to perform hypothesis testing or statistical comparison, and that all analyses will be descriptive in nature • Revised the definitions of DFS and TTR to start from the time of randomization for both CR and NCR patients at the 3-month Visit • Deleted the exploratory endpoint of other resource utilization • Removed data review committee • Removed ET Visit from SoA and clarified that patients who discontinue from the study should have an EOS Visit performed	[redacted]

Version	Date	Description of Changes	Brief Rationale
2.0	20 Dec 2021	• Updated Study BL005 from preliminary to final data • Added COVID-19 to the study risk assessment • Defined sexual abstinence and clarified that periodic abstinence is not an acceptable method of contraception • Clarified that hospitalization is not a requirement for the study • Clarified that access to treatment information by Sponsor personnel will be restricted by role • Clarified that patients with disease progression at the 3-month Visit or subsequent follow-up visits will be considered to have completed the study at that time • Revised Section 8.2.2 and added a new Appendix 1 (Guidance on Evaluation of Response) • Clarified that rectal examination (part of urology-oriented PE at Screening Visit) applies to both male and female patients • Deleted a planned supportive analysis of the primary endpoint based on propensity scores • Reorganized the protocol appendices to follow Section 11 (References)	[redacted]