# Title Page

**Protocol Title:** A Phase 3b, Open-Label, Single-Arm, Multicenter Study to Assess the Feasibility of Home Instillation of UGN-102 for Treatment of Patients with Low-Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence

**Protocol Number:** BL010

**Compound:** UGN-102 (mitomycin) for intravesical solution

**Study Phase:** 3b

**Sponsor Name:** UroGen Pharma Ltd.

**Legal Registered Address:**
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**Regulatory Agency Identifier Number(s):**
IND 138749

| Protocol Status | Version | Date |
|---|---|---|
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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.

# 1. Protocol Summary

## 1.1. Synopsis

**Protocol Title:** A Phase 3b, Open-Label, Single-Arm, Multicenter Study to Assess the Feasibility of Home Instillation of UGN-102 for Treatment of Patients with Low-Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence

**Overall Design:** This Phase 3b, open-label, single-arm, multicenter study is designed to assess the feasibility of home instillation of UGN-102 (mitomycin) for intravesical solution in approximately 10 patients with low-grade (LG) intermediate risk (IR) non-muscle-invasive bladder cancer (NMIBC).

The primary objective of this study is to evaluate the feasibility of home instillation of UGN-102 as an alternative to instillation in a clinical setting. Feasibility will be assessed by evaluation of safety and tolerability, rate of discontinuation from at home study treatment, and feedback from patients, home health professionals, and investigators via standardized questionnaires. The secondary objective of this study is to evaluate the efficacy of UGN-102 for the treatment of LG IR NMIBC following home instillation. Efficacy will be assessed at the 3-month Visit (3 months after the first instillation of UGN-102) by complete response rate (CRR), defined as the proportion of patients who achieved complete response (CR) as determined by cystoscopy, for cause biopsy, and urine cytology.

Patients who provide informed consent will undergo a Screening Visit to determine eligibility. Approximately 10 patients ≥ 18 years of age with LG IR NMIBC who meet the eligibility criteria will receive 6 once weekly intravesical instillations of UGN-102. The first instillation will be performed at the investigative site and subsequent instillations will be performed at the patient's home by a properly trained and qualified home health professional.

End-of-study (EOS) is defined as the last patient last visit (LPLV). The EOS will be declared after all patients have completed the 3-month Visit (7 weeks ± 1 week after the final instillation of UGN-102).

Following the 3-month Visit, all patients will exit the study and continue with standard of care according to their treating physician.

**Objectives and Endpoints:**

| Objective | Endpoints |
|---|---|
| Primary | |
| To evaluate the feasibility of home instillation of UGN-102 for treatment of patients with LG IR NMIBC | Feasibility will be assessed by evaluation of:<br>• Safety and tolerability<br>  o Reporting of AEs, including SAEs and AESIs<br>  o Standard clinical laboratory tests (hematology, serum chemistry, and urinalysis)<br>  o Physical examination and vital sign measurements<br>• Rate of discontinuation from at home study treatment |

| Objective | Endpoints |
|---|---|
| | • Feedback from patients, home health professionals, and investigators via standardized questionnaires |
| Secondary | |
| To evaluate the efficacy of UGN-102 for treatment of LG IR NMIBC following home instillation with respect to complete response rate (CRR) at the 3-month disease assessment | CRR is defined as the proportion of patients who achieved CR at the 3-month Visit (3 months after the first instillation of study treatment) as determined by cystoscopy, for cause biopsy, and urine cytology |

AE = adverse event; AESI = adverse event of special interest; CR = complete response; CRR = complete response rate; LG IR NMIBC = low-grade intermediate risk non-muscle-invasive bladder cancer; SAE = serious adverse event.

**Inclusion Criteria:**

1. Capable of giving written 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 ICF.
3. Patient who has newly diagnosed or historic LG NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening.
4. Has IR disease, defined as having 1 or 2 of the following:
   - presence of multiple tumors.
   - solitary tumor > 3 cm.
   - recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis at the initial Screening Visit).
5. Negative voiding cytology for high-grade (HG) disease within 6 weeks before Screening.
6. Has adequate organ and bone marrow function as determined by routine laboratory tests as below:
   - Leukocytes ≥ 3,000/μL (≥ $3\times10^9$/L).
   - Absolute neutrophil count ≥ 1,500/μL (≥ $1.5\times10^9$/L).
   - Platelets ≥ 100,000/μL (≥ $100\times10^9$/L).
   - Hemoglobin ≥ 9.0 g/dL.
   - Total bilirubin ≤ 1.5 × upper limit of normal (ULN).
   - Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤ 2.5 × ULN.
   - Alkaline phosphatase (ALP) ≤ 2.5 × ULN.
   - Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min.
7. Has no evidence of active urinary tract infection (UTI) at the Screening and baseline visits.
8. Patient is willing to receive instillations of UGN-102 at home (ie, Treatment Visits 2 to 6) by an appropriately trained home health professional.

9. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for clinical study participants. Women of childbearing potential (defined as premenopausal women who have not been sterilized), including female patients and female partners of male patients, must be willing to use 2 acceptable forms of effective contraception from first instillation through 6 months post treatment. Acceptable methods of birth control that are considered to have a low failure rate (ie, less than 1% per year) when used consistently and correctly include implants, injections, combined (estrogen/progesterone) oral contraceptives, intrauterine devices (only hormonal), condoms with spermicide, sexual abstinence, or vasectomized partner.
10. Has an anticipated life expectancy of at least the duration of the trial.

**Exclusion Criteria:**

1. Received Bacillus Calmette-Guérin (BCG) treatment for urothelial carcinoma (UC) within previous 1 year.
2. History of HG bladder cancer (papillary or carcinoma in situ) in the past 2 years.
3. Known allergy or sensitivity to mitomycin that in the Investigator's opinion cannot be readily managed.
4. Clinically significant urethral stricture that would preclude passage of a urethral catheter.
5. History of:
   - neurogenic bladder.
   - active urinary retention.
   - any other condition that would prohibit normal voiding.
6. Past or current T1 UC, muscle invasive UC (ie, T2, T3, T4), metastatic UC, or concurrent upper tract urothelial carcinoma (UTUC).
7. 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.
8. History of prior treatment with an intravesical chemotherapeutic agent in the past 2 years except for a single dose of chemotherapy immediately after any previous transurethral resection of bladder tumors (TURBT).
9. Has participated in a study with an investigational agent or device within 30 days of enrollment.

**Number of Patients:** Approximately 10 patients will be enrolled and treated in this study.

**Number of Investigative Sites:** The study will be conducted at approximately 5 investigative sites in the US.

**Qualified Health Care Personnel:** The study will be conducted by appropriately trained urologists and qualified home health professionals. Clinical nurse educators (CNEs) will train pharmacy personnel on study treatment preparation and study personnel (eg, investigators and home health professionals) on the UGN-102 instillation procedure.

**Treatment and Duration:** Eligible patients will be treated with 6 once-weekly intravesical instillations of UGN-102 (75 mg mitomycin in 56 mL admixture; 1.33 mg mitomycin per 1 mL of admixture).

**Data Review Committee:** None.

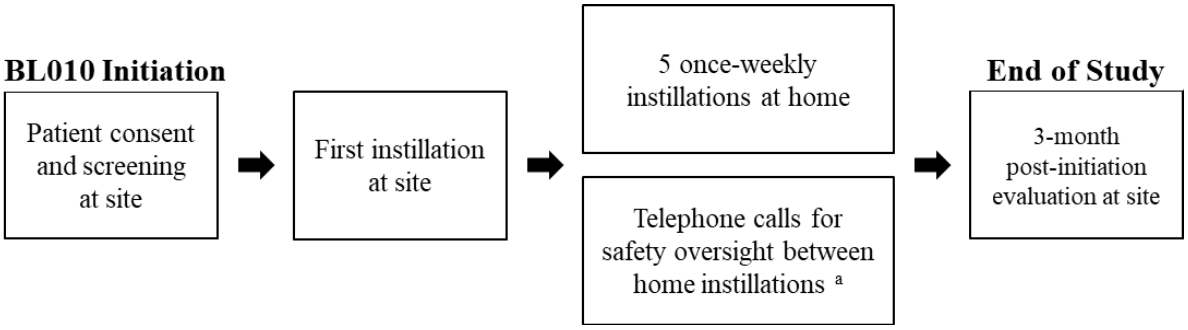
**Statistical Analyses:** No formal hypothesis will be tested. The sample size of this study (approximately 10 patients) is based on feasibility.

Safety data will be analyzed descriptively. Point estimates of the secondary endpoint CRR at the 3-month Visit along with the exact 95% confidence interval (CI) will be summarized.

The Safety Analysis Set that includes all patients who received any dose of UGN-102 will serve as the primary population for the analyses of safety and efficacy data in this study.

No interim analysis will be conducted. The final analysis will be performed after all patients complete the end of study visit or are withdrawn from the study.

## 1.2. Schema




a. One day after every home instillation (+1 day).

## 1.3. Schedule of Activities

| Procedures | Screening Period [a] | Treatment Visit 1 (Baseline) | Treatment Visit 2 | Treatment Visit 3 | Treatment Visit 4 | Treatment Visit 5 | Treatment Visit 6 | 3-month Visit (EOS) | ET |
|---|---|---|---|---|---|---|---|---|---|
| **Planned Location** | **Clinic** | **Clinic** | **Home** | **Home** | **Home** | **Home** | **Home** | **Clinic** | **Clinic** |
| **Day/Week/Month** | **D-14 to D-1 or D-28 to D-1** | **D1/W1** | **D8/W2** | **D15/W3** | **D22/W4** | **D29/W5** | **D36/W6** | **3 months (7 weeks ±1 week after final instillation)** | **NA** |
| **Window [b]** | **NA** | **D-1 +1/+7 d** | **-1/+3 d** | **-1/+3 d** | **-1/+3 d** | **-1/+3 d** | **-1/+3 d** | **±1 week** | **NA** |
| Informed consent | X [c] | | | | | | | | |
| Inclusion/exclusion criteria | X | | | | | | | | |
| Demographics | X | | | | | | | | |
| Medical/surgical & smoking history | X | | | | | | | | |
| Concomitant medication review | X [d] | X | X | X | X | X | X | X | X |
| Full physical examination [e] | X | | | | | | | | |
| Urological examination [f] | X | X | | | | | | X | X |
| Clinical assessment before study drug instillation [g] | | | X | X | X | X | X | | |
| Height and weight | X | | | | | | | | |
| Vital signs [h] | X | X | X | X | X | X | X | X | X |
| Hematology/serum chemistry [i] | X | X | | | | | | X | X |
| Urinalysis [j] | X | X | X | X | X | X | X | X | X |
| Pregnancy test (WOCBP only) [k] | X | | | | | | | X | X |
| Adverse event review and evaluation [l] | X | X | X | X | X | X | X | X | X |
| CT Urogram, retrograde pyelogram, or MRI [m] | X | | | | | | | | |
| Cold cup biopsy [n] | X | | | | | | | | |
| Cystoscopy (white light) | X | | | | | | | X | |
| Urine cytology | X [o] | | | | | | | X | |
| Administer study treatment [p] | | X | X | X | X | X | X | | |
| Patient questionnaire [q] | | | X | X | X | X | X | X | X |
| Home health professional questionnaire [r] | | | X | X | X | X | X | | |
| Investigator questionnaire [s] | | | | | | | | X | X |
| Telephone call for safety oversight after home instillation [t] | | | X | X | X | X | X | | |
| Biopsy remaining lesions if indicated by cystoscopy | | | | | | | | X [u] | |
| Disease Assessment | | | | | | | | X [u] | |
| Study Exit | | | | | | | | X [v] | |
| Complete eCRFs | X | X | X | X | X | X | X | X | X |

AE = adverse event; AESI = adverse event of special interest; CT = computed tomography; d = day; D = visit day; eCRF = electronic case report form; EOS = end-of-study; ET = early termination; HG = high-grade; ICF = informed consent form; LG = low-grade; MRI = magnetic resonance imaging; NA = not applicable; NMIBC = non-muscle-invasive bladder cancer; SAE = serious adverse event; UC = urothelial carcinoma; UTUC = upper tract urothelial carcinoma; W = visit week; WOCBP = women of child-bearing potential.

a. The Screening Period is up to 14 days for patients who do not need a Screening biopsy and up to 28 days for patients who need a Screening biopsy. Screening procedures are required to provide evidence of LG NMIBC and no evidence of HG disease.
b. Windows are provided to accommodate patient logistics in scheduling. Treatment instillations should occur 6 to10 days apart. Every effort should be made to minimize the time interval between diagnosis and Treatment Visit 1 (the maximum interval from end of Screening to first instillation should be ≤ 7 days).
c. Obtain written informed consent before any study-related procedures are performed.
d. Any past therapy (eg, pharmacological or surgical interventions) related to UC will be recorded during Screening.
e. A full physical examination will be performed at the Screening Visit by a physician at the investigative site (Section 9.3.1). Additional full physical examinations may be performed during the study if clinically indicated.
f. A urological examination will be performed at the Screening Visit, Treatment Visit 1, and at the 3-month Visit (or ET) by a physician at the investigative site (Section 9.3.1). The urological examination should be performed before cystoscopy at relevant visits. Additional urological examinations may be performed during the study if clinically indicated. Any clinically relevant changes in urological examinations will be recorded on the AE sections of the eCRF.
g. Clinical assessment will be performed before study drug instillation. Body systems to be reviewed include general appearance and urethral meatus (Section 9.3.1). Abnormal findings observed at home instillation visits will be documented and reported by the home health professional to the investigative site during the visit.
h. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure (Section 9.3.2).
i. Hematology and serum chemistry samples will be tested at the local laboratory. Parameters to be analyzed in this study are listed in Section 9.3.3. Other parameters that are part of the local laboratory standard panel may be reported in addition to the protocol-specified parameters.
j. Dipstick on-site and at home; culture and sensitivity added at Screening, and when otherwise clinically indicated, if suggestive for infection (at local laboratory) (Section 9.3.4).
k. Urine or serum pregnancy test (at local laboratory). See Section 9.3.5 for the definition of a female of childbearing potential.
l. Adverse events will be collected from the signing of the ICF until the 3-month Visit (EOS). 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 9.4.1, Section 9.4.5, and Section 9.4.6. Investigators are to report AEs (including AESIs) in a consistent manner as described in Section 9.4.2.
m. CT Urogram, retrograde pyelogram, or MRI (if other tests are contraindicated) to rule out UTUC (acceptable if performed within 6 months before Screening Visit) (results assessed locally).
n. A single representative cold cup biopsy to confirm LG tumor will be performed only if not already performed within 8 weeks before Screening Visit. This is a diagnostic biopsy to demonstrate histopathology of tumor and resection of the tumor is not to performed.
o. No cytology needed if results from a prior cytology within 6 weeks before Screening are available.
p. Treatment Visit 1 will occur at the investigative site and study treatment instillation will be performed by a qualified physician. Treatment Visits 2 to 6 will occur at the patient's home and study treatment instillation will be performed by a properly trained and qualified home health professional. The patient will be monitored for AEs during and for at least 60 minutes after each study treatment instillation. If the patient withdraws consent for in-home instillation of study treatment, the patient may continue treatment and scheduled assessments at the investigative site (Section 8.1.3). Administration of study treatment will be documented in the patient file, eCRF, and in the Drug Administration Records (Section 7.1.3.1).
q. Patient questionnaire: Part 1 must be completed after home instillation of study treatment at Treatment Visits 2 to 6; Part 2 must be completed at the 3-month Visit (EOS) or ET Visit) (Appendix A).
r. Home health professional questionnaire: Part 1 must be completed after home instillation of study treatment at Treatment Visits 2 to 6; Part 2 must be completed after home instillation of study treatment at Treatment Visits 3 to 6 (Appendix B).
s. Investigator questionnaire: Must be completed at the 3-month Visit (EOS) or ET Visit (Appendix C).
t. The home health professional will call the patient 1 day (+1 day) after each home instillation of study treatment to monitor for safety (Section 7.1.3.1).
u. Efficacy assessment (approximately 3 months after the first instillation of study treatment). Biopsies may be needed at the 3-month Visit (EOS) if any remaining lesions are visualized during cystoscopy (Section 9.2).
v. Following the 3-month Visit, all patients will exit the study and continue with standard of care according to their treating physician.

## Abbreviations

| | |
|---|---|
| ADL | activities of daily living |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BCG | Bacillus Calmette-Guérin |
| CBC | complete blood count |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| CNE | clinical nurse educator |
| CR | complete response |
| CRR | complete response rate |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCR | durable complete response |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| eGFR | estimated glomerular filtration rate |
| EOS | end-of-study |
| ET | early termination |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HG | high-grade |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IP | investigational products |
| IR | intermediate risk |
| IRB | Institutional Review Board |
| LG | low-grade |
| LPLV | last patient last visit |
| LUTS | lower urinary tract symptoms |
| MedDRA | Medical Dictionary for Regulatory Activities |

| | |
|---|---|
| NCR | non-complete response |
| NDD | no detectable disease |
| NMIBC | non-muscle-invasive bladder cancer |
| PI | Principal Investigator |
| PQC | product quality complaint |
| PT | preferred term |
| QC | quality control |
| QTL | quality tolerance limit |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SEER | Surveillance, Epidemiology, and End Results (Program) |
| SMP | Study Monitoring Plan |
| SoA | Schedule of Activities |
| SRT | safety review team |
| SUSAR | suspected unexpected serious adverse reaction |
| TEAE | treatment-emergent adverse event |
| TURBT | transurethral resection of bladder tumors |
| UADR | unexpected adverse drug reaction |
| UC | urothelial carcinoma |
| ULN | upper limit of normal |
| US | United States |
| USP | United States Pharmacopeia |
| UTI | urinary tract infection |
| UTUC | upper tract urothelial carcinoma |

# 2. Introduction

### Non-Muscle-Invasive Bladder Cancer

Bladder cancer is the sixth most common cancer in the US, with an expected 81,000 new cases diagnosed in 2020 (ACS, 2020). At the time of diagnosis, 75% of patients present with NMIBC (Babjuk et al, 2019; Monteiro et al, 2019). NMIBC includes a clinically heterogeneous group of cancers with a wide range of recurrence and progression probabilities (Chang et al, 2016). Therefore, treatment guidelines recommend classifying patients with NMIBC as being at low, intermediate, or high risk of disease recurrence and/or progression (Babjuk et al, 2019; Chang et al, 2016; Kamat et al, 2014). While the management of low risk and high-risk patients appears clear, the best treatment option for intermediate risk patients remains undefined (Monteiro et al, 2019). Based on analysis of the Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database, UroGen estimates that LG IR NMIBC represents approximately 25% of newly diagnosed bladder cancer cases in the US (SEER Program, 2019).

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

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

### UGN-102

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

mitomycin over a period of 4 to 6 hours. The prolonged exposure of tumor cells to mitomycin leads to improved chemoablation compared with aqueous preparations of mitomycin.

The efficacy and safety of UGN-102 for the treatment of patients with LG IR NMIBC was evaluated in a Phase 2b, single-arm, multicenter study (BL005). Intravesical instillation of UGN-102 once weekly for 6 weeks resulted in high rates of CR at 3 months and durable complete response (DCR) at 12 months after the start of study treatment. A total of 63 patients were enrolled and treated with UGN-102. Forty-one (65.1%) patients achieved the primary endpoint of CR at 3 months after the first instillation of UGN-102 (95% CI of CR rate: 52.0, 76.7), and 25/41 (61.0%) patients had a DCR at 12 months after the first instillation (95% CI of DCR rate: 44.5, 75.8). The 9-month duration of response rate as estimated by the Kaplan-Meier method was 72.5% (95% CI: 54.4, 84.3), ie, the probability that a patient will maintain CR for at least 9 months is 72.5%. The overall safety profile of UGN-102 was favorable, with primarily mild to moderate adverse events (AEs), no treatment-related serious adverse events (SAEs) or hospitalizations, low number of treatment discontinuations, and no clinically meaningful trends or pattern of changes identified in laboratory parameters, vital signs, or physical examinations.

Based on the favorable tolerability profile and the vulnerability of this patient population, the intent of this study is to demonstrate that UGN-102 may be safely and feasibly administered in the home setting.

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

## 2.1. Study Rationale

This study aims to demonstrate that home instillation of UGN-102 is a feasible alternative to instillation in a clinical setting. Potential advantages of home instillation include but are not limited to:

- moving healthcare out of the clinical setting and into a patient's home, potentially reducing hospital resource utilization.
- decreased risk of exposure to infections observed in the healthcare setting.
- simplifying travel logistics, decrease travel expenditures, decrease clinic waiting periods for the patient.
- decreased burden to family members who might otherwise need to transport patient to and from clinical setting.
- receiving cancer treatment in a familiar environment.

## 2.2. Benefit-Risk Assessment

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

### 2.2.1. Risk Assessment

**Cystitis and Lower Urinary Tract Symptoms**

Cystitis and other lower urinary tract symptoms (LUTS) may develop. These symptoms are well known in relation to standard mitomycin instillations and are not specific to UGN-102. Urine tests, including urinalysis and urine culture as indicated, will be checked regularly during the study to monitor for potential UTI. Any signs and/or symptoms of UTI will be treated by the Investigator according to local practice.

**Toxicity Associated with Systemic Absorption/Local Irritation**

Bladder toxicity and rarely bone marrow toxicity (thrombocytopenia and leukopenia) are considered possible risks for patients when mitomycin is administered topically. Complete blood count and renal and liver function tests will be checked during the study (Table 4), and the Investigator will follow any clinically significant abnormality until it is resolved, stabilized, or otherwise managed (Section 9.3.3).

**Allergic Response to Mitomycin**

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

**Instillation Procedure**

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

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

The first study treatment instillation will be performed at the investigative site by a qualified physician. Treatment Visits 2 to 6 will occur at the patient's home and study treatment instillation will be performed by a properly trained and qualified home health professional. To the extent possible, the same home health professional will perform home instillation of study treatments for a given patient.

If the assigned home health professional is unable to perform the study treatment instillation on a scheduled dose day, another trained and qualified home health professional will perform the required study treatment instillation (Section 7.1.3.1).

The patient will be monitored for AEs during and for at least 60 minutes after each study treatment instillation.

### 2.2.2. Benefit Assessment

The potential advantages of instillation of mitomycin in hydrogel include:

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

These characteristics of UGN-102 (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.

**Instillation Procedure**

Potential benefits of providing medical care at home include patient convenience, comfort and logistical ease, decreased risk of nosocomial infections, decreased exposure to others who may transmit infections such as the COVID-19 virus, influenza, or common “cold” virus (eg, rhinoviruses and adenoviruses), and decreased burden on family members who might otherwise be responsible for transporting patients to and from procedures. Other potential benefits include increased patient engagement and compliance in study procedures.

### 2.2.3. Overall Benefit-Risk Conclusion

Overall, based on the efficacy and safety results observed to date, UGN-102 has a favorable benefit-risk profile for the treatment of LG IR NMIBC. Additionally, based on the favorable tolerability profile and the vulnerability of this patient population, home instillation of UGN-102 may be a feasible treatment paradigm and offer potential advantages compared with instillation in a clinical setting.

# 3. Objectives and Endpoints

| Objective | Endpoints |
|---|---|
| Primary | |
| To evaluate the feasibility of home instillation of UGN-102 for treatment of patients with LG IR NMIBC | Feasibility will be assessed by evaluation of:<br>• Safety and tolerability<br>  o Reporting of AEs, including SAEs and AESIs<br>  o Standard clinical laboratory tests (hematology, serum chemistry, and urinalysis)<br>  o Physical examination and vital sign measurements<br>• Rate of discontinuation from at home study treatment<br>• Feedback from patients, home health professionals, and investigators via standardized questionnaires |
| Secondary | |
| To evaluate the efficacy of UGN-102 for treatment of LG IR NMIBC following home instillation with respect to complete response rate (CRR) at the 3-month disease assessment | CRR is defined as the proportion of patients who achieved CR at the 3-month Visit (3 months after the first instillation of study treatment) as determined by cystoscopy, for cause biopsy, and urine cytology |

AE = adverse event; AESI = adverse event of special interest; CR = complete response; CRR = complete response rate; LG IR NMIBC = low-grade intermediate risk non-muscle-invasive bladder cancer; SAE = serious adverse event.

# 4. Study Design

## 4.1. Overall Design

This Phase 3b, open-label, single-arm, multicenter study is designed to assess the feasibility of home instillation of UGN-102 (mitomycin) for intravesical solution in approximately 10 patients with LG IR NMIBC.

The primary objective of this study is to evaluate the feasibility of home instillation of UGN-102 as an alternative to instillation in a clinical setting. Feasibility will be assessed by evaluation of safety and tolerability, rate of discontinuation from at home study treatment, and feedback from patients, home health professionals, and investigators via standardized questionnaires. The secondary objective of this study is to evaluate the efficacy of UGN-102 for the treatment of LG IR NMIBC following home instillation. Efficacy will be assessed at the 3-month Visit (3 months after the first instillation of UGN-102) by CRR, defined as the proportion of patients who achieved CR as determined by cystoscopy, for cause biopsy, and urine cytology.

Patients who provide informed consent will undergo a Screening Visit to determine eligibility. The Screening Period is up to 14 days for patients who do not need a Screening biopsy and up to 28 days for patients who need a Screening biopsy. Screening procedures are required to provide evidence of LG NMIBC and to rule out evidence of HG disease (Section 1.3).

A single representative cold cup biopsy to confirm LG tumor will be performed only if not already performed within 8 weeks before Screening. This is a diagnostic biopsy to demonstrate the histopathology of the tumor, and resection of tumor is not to be performed (Section 1.3).

Patients will receive 6 once weekly intravesical instillations of study treatment. The first instillation will be performed at the investigative site and subsequent instillations will be performed at the patient's home by a properly trained and qualified home health professional. The home health professional will call the patient 1 day (+1 day) after each home instillation of study treatment to monitor for safety (Section 1.3).

The UGN-102 concentration to be used in this study will be 1.33 mg mitomycin per 1 mL admixture. The volume of UGN-102 admixture to be instilled will be 56 mL (75 mg of mitomycin) (Section 7.1.3).

At each home instillation visit, the patient and home health professional will complete a feasibility questionnaire. In addition, the patient and investigator will complete a feasibility questionnaire at the 3-month Visit (EOS) or ET Visit (Section 1.3 and Section 9.9).

Patients will return to the clinic for the 3-monthVisit (7 weeks ± 1 week after the final instillation of UGN-102) for determination of response to treatment.

Response to study treatment will be determined based on visual evaluation by cystoscopy (white light) (appearance, number, and size of any remaining lesions), interpretation of urine cytology, and for cause biopsy and histopathology of any remaining lesions (Section 9.2.2). Any lesions or suspect tissue must be biopsied to evaluate for persistence of disease.

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

Safety will be evaluated based on vital signs, 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 9.4.1.3.3), and qualified per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) as Grade 3 or 4 (Section 9.4.1.3.1).

A patient will be considered to have completed the study if the patient completes the 3-month Visit in accordance with the Schedule of Activities (SoA) (Section 1.3).

Following the 3-month Visit, all patients will exit the study and continue with standard of care according to their treating physician.

End-of-study is defined as the LPLV. The EOS will be declared after all patients have completed the 3-month Visit.

## 4.2. Scientific Rationale for Study Design

UroGen estimates that LG IR NMIBC represents approximately 25% of newly diagnosed bladder cancer cases in the United States (SEER Program, 2019). While TURBT remains the current surgical standard of care for treatment of LG IR NMIBC (NCCN, 2020, Chang et al, 2016), Study BL005 (OPTIMA II) showed a favorable efficacy and safety profile with 6 once weekly intravesical instillations of UGN-102 (75 mg mitomycin) as an alternative to surgery, and demonstrated durable clinical response in patients with LG IR NMIBC (Huang et al, 2020).

Intravesical instillation of UGN-102 may become a viable alternative to TURBT for these patients and is under evaluation in a Phase 3 study (BL006). One of the benefits of UGN-102 is the ability to safely administer in the outpatient setting by personnel trained in bladder catheterization with appropriate physician oversight. This study aims to demonstrate that home instillation of UGN-102 is a feasible alternative to instillation in a clinical setting, which might mitigate some of the challenges in the patient experience (logistical, expense, and comfort) when receiving treatment for LG IR NMIBC.

The COVID-19 pandemic has created an unprecedented need to re-evaluate the entirety of global healthcare and specifically the cancer care delivery system. Home instillation of antitumor therapy is not new outside the US, and internationally approximately 5%-10% of patients diagnosed with a range of cancers receive antitumor therapy at home (Lal et al, 2013; Luthi et al, 2012; Innominato et al, 2016). This global practice could be considered a model for feasibility in the US for in-home antitumor therapy delivery. Pointedly so during an unprecedented time when in-home consultation and care are increasingly sought, becoming familiar to patients, and recognizably viable by both the patient and the healthcare provider; all thereby, mitigating increased risk of morbidity and mortality from COVID-19 and other readily transmissible infectious diseases (Handley and Bekelman, 2019; Handley et al, 2020; Laughlin et al, 2020; Dai et al, 2020).

A re-evaluation of in-home delivery of cancer treatments in the US is not only a reasonable task during the current pandemic, but a potential viable option for post-pandemic practice leading to care that benefits the overall health, well-being and safety of patients diagnosed with certain cancers. Intravesical catheterization delivery of immunotherapy has been performed by trained medical professionals for superficial bladder cancer for over 45 years (Fuge et al, 2015). Thus, the procedure is foundational and having the flexibility to receive treatment by a trained and qualified home health professional at home may change the landscape of LG NMIBC treatment.

Further, feasibility for in-home treatment instillation of UGN-102 may be tested in this subpopulation of cancer patients given that LG IR NMIBC has a well-understood clinical behavior over time (Marcq et al, 2019; Hurle et al, 2018; Tiu et al, 2014) and the recent promising results of the OPTIMA II trial (Huang et al, 2020).

## 4.3. Justification for Dose

The UGN-102 dose of 75 mg was chosen based on both efficacy and tolerability. Study BL003 demonstrated a 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 and a higher rate of AEs than the 75 mg dose in Study BL003. Study BL005 showed a favorable efficacy and safety profile with 6 once weekly instillations of 75 mg UGN-102. Results showed a considerable treatment response with encouraging durability. The overall safety profile of UGN-102 was favorable, with primarily mild to moderate AEs, no treatment-related SAEs or hospitalizations, low number of treatment discontinuations, and no clinically meaningful trends or pattern of changes identified in laboratory parameters, vital signs, or physical examinations.

## 4.4. End-of-Study Definition

EOS will be declared after all patients have completed the 3-month Visit (7 weeks ± 1 week after the final instillation of UGN-102).

The EOS is defined as LPLV.

# 5. Study Population

Adult patients with LG IR NMIBC who are willing to undergo study treatment at home will be enrolled in the study.

## 5.1. Inclusion Criteria

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

1. Capable of giving written informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.
2. Patient must be ≥ 18 years of age, at the time of signing the ICF.
3. Patient who has newly diagnosed or historic LG NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening.
4. Has IR disease, defined as having 1 or 2 of the following:
   - presence of multiple tumors.
   - solitary tumor > 3 cm.
   - 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 before Screening.

6. Has adequate organ and bone marrow function as determined by routine laboratory tests as below:
    - Leukocytes ≥ 3,000/μL (≥ $3\times10^9$/L).
    - Absolute neutrophil count ≥ 1,500/μL (≥ $1.5\times10^9$/L).
    - Platelets ≥ 100,000/μL (≥ $100\times10^9$/L).
    - Hemoglobin ≥ 9.0 g/dL.
    - Total bilirubin ≤ 1.5 × ULN.
    - AST/ALT ≤ 2.5 × ULN.
    - ALP ≤ 2.5 × ULN.
    - eGFR ≥ 30 mL/min.
7. Has no evidence of active urinary tract infection at the Screening and baseline visits.
8. Patient is willing to receive instillations of UGN-102 at home (ie, Treatment Visits 2 to 6) by an appropriately trained home health professional.
9. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for clinical study participants. Women of childbearing potential (defined as premenopausal women who have not been sterilized), including female patients and female partners of male patients, must be willing to use 2 acceptable forms of effective contraception from first instillation through 6 months post treatment. Acceptable methods of birth control that are considered to have a low failure rate (ie, less than 1% per year) when used consistently and correctly include implants, injections, combined (estrogen/progesterone) oral contraceptives, intrauterine devices (only hormonal), condoms with spermicide, sexual abstinence, or vasectomized partner.
10. Has an anticipated life expectancy of at least the duration of the trial.

## 5.2. Exclusion Criteria

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

1. Received BCG treatment for UC within previous 1 year.
2. History of HG bladder cancer (papillary or carcinoma in situ) in the past 2 years.
3. Known allergy or sensitivity to mitomycin that in the Investigator's opinion cannot be readily managed.
4. Clinically significant urethral stricture that would preclude passage of a urethral catheter
5. History of:
    - neurogenic bladder.
    - active urinary retention.
    - any other condition that would prohibit normal voiding.

6. Past or current T1 UC, muscle invasive UC (ie, T2, T3, T4), metastatic UC, or concurrent UTUC.
7. 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.
8. History of prior treatment with an intravesical chemotherapeutic agent in the past 2 years except for a single dose of chemotherapy immediately after any previous TURBT.
9. Has participated in a study with an investigational agent or device within 30 days of enrollment.

## 5.3. Lifestyle Considerations

Not applicable.

## 5.4. Screen Failures

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

## 5.5. Strategies for Recruitment and Retention

A sufficient number of patients will be screened to ensure that approximately 10 patients with LG IR NMIBC are enrolled in the study. Patients who discontinue before the EOS Visit may be replaced at the Sponsor's discretion. The study will be conducted at approximately 5 investigative sites in the US that provide care to patients with bladder cancer.

## 5.6. Criteria for Temporarily Delaying Administration of Study Treatment

If at any time during the study the Investigator identifies myelosuppression, evidence of an active UTI, or any other significant clinical event or laboratory derangements outside the pre-defined parameters, treatment may be postponed for up to 4 weeks until the clinical event resolves and/or laboratory values improve (Section 9.3.3.1).

# 6. Qualified Health Care Personnel

The study will be conducted by appropriately trained urologists, clinical nurse educators (CNEs), and qualified home health professionals.

## 6.1. Clinical Nurse Educators

This study will contract CNEs to train pharmacy personnel on study treatment preparation and study personnel (eg, investigators and home health professionals) on the UGN-102 instillation procedure. The role of the CNE in the current study will include, but may not be limited to:

- conduct training on UGN-102 instillation procedures for the Principal Investigator, sub-investigator(s), home health professionals, and other relevant personnel before the first study treatment administration.
- be present for training purposes during the first study treatment administration.
- conduct training for pharmacy personnel on UGN-102 study treatment preparation as per the Instructions for Pharmacy.
- following training, attend the first pharmacy preparation, if allowed by the pharmacy.
- attend at least the first study treatment administration at the patient's home.

## 6.2. Home Health Professionals

This study will contract licensed home health professionals to administer the study treatment at the patient's home for Treatment Visits 2 to 6. The role of the home health professional at each home visit will include, but may not be limited to:

- communicate with site study team and coordinate patient's home visits for study treatment administration.
- attend the patient's first treatment at the investigational study site.
- attend the patient's home for subsequent instillations per training.
- coordinate study drug and study supplies to be available at the patient's home for home administration.
- conduct a clinical assessment, measure vital signs, and document the findings in the electronic Case Report Form (eCRF).
- review concomitant medications.
- review adverse events and monitor patient for AEs for at least 60 minutes post-instillation.
- call the patient approximately 24 hours after instillation to see how the patient is feeling and if there are any reported adverse events.
- remove all study-related hazardous waste from the patient's home at the end of the home visit.

# 7. Study Treatment

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

## 7.1. Study Treatment Administered

### 7.1.1. 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 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. For Treatment Visits 2 to 6, the assigned courier will obtain the prepared UGN-102 admixture from the site's pharmacy and deliver it to qualified home health professional at the patient's home for instillation.

The UGN-102 single dose carton contains the below listed components (Table 1).

**Table 1 UGN-102 Components**

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

WFI = water for injection.

a For the proposed indication, each 40 mg vial of 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-metho3xymitosane
Formula: $C_{15}H_{18}N_4O_5$
Molecular weight: 334.33 g/mol
CASRN: 50-07-7

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

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

**Table 2 Vial Composition of Mitomycin for Solution**

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

USP = United States Pharmacopeia.

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

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

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

### 7.1.2. Preparation and Administration Ancillary Supplies

Ancillary supplies used to prepare and administer the study treatment are detailed in the Instructions for Pharmacy and Instructions for Administration. Home health professionals will also be provided with a carrying bag containing commercially available ancillary items necessary for home instillation of study treatment as detailed in the Study Distribution Manual.

### 7.1.3. Administration and Dosing

#### 7.1.3.1. Administration

Patients will receive 6 once weekly intravesical instillations of study treatment.

Treatment Visit 1 will occur at the investigative site and study treatment instillation will be performed by a qualified physician.

Treatment Visits 2 to 6 will occur at the patient's home and study treatment instillation will be performed by a properly trained and qualified home health professional (Section 6). To the extent possible, the same home health professional will perform home instillation of study treatments for a given patient.

If the assigned home health professional is unable to perform the study treatment instillation on a scheduled dose day, another trained and qualified home health professional will perform the required study treatment instillation.

The patient will be monitored for AEs during and for at least 60 minutes after each study treatment instillation.

The home health professional will call the patient 1 day (+1 day) after each home instillation of study treatment to monitor for safety.

Study treatment administration will be documented in the patient file, eCRFs, and in the Drug Administration Records.

#### 7.1.3.2. Dosing

| 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 for detailed instillation instructions.

## 7.2. UGN-102 Single Dose Carton /Handling/Storage/Accountability

### 7.2.1. Acquisition and Accountability

UGN-102 single-dose carton is assembled for UroGen Pharma Ltd. 9 Ha'Ta'asiya St., Ra'anana, Israel by [redacted] All clinical supplies will be packaged and labeled in compliance with GMP guidelines. The shipment process should comply with the rules of Good Distribution Practices. Before shipment of clinical supplies, the Sponsor or Sponsor's Designee should notify the Principal Investigator (PI) regarding the anticipated date of arrival at the hospital/clinic pharmacy. The IP will be sent to the site only after study approval by the 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 7.2.5. The impacted IP must be marked "not for use" and quarantined during investigation until a decision has been made regarding the drug's validity.

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

Unused UGN-102 must be available for verification by the Sponsor's site monitor during on-site monitoring visits. Unused or expired UGN-102 returned to the Sponsor must be documented on the drug return form.

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

Unusable UGN-102 single dose cartons will be marked "not for use" in pen over the label and stored separately from usable UGN-102 single dose cartons.

Replacement UGN-102 will be supplied after request for additional supplies has been issued to the Sponsor's Designee.

Following completion of drug accountability by the clinical research associate, used study treatment vials should be discarded locally according to local institution guidelines for cytotoxic waste destruction. Discarding/destruction of the used UGN-102 admixture vials must be documented in the drug disposal form.

### 7.2.2. Formulation, Appearance, Packaging, and Labeling

The formulation of the study treatment and the contents of UGN-102 is described in Section 7.1.1. All clinical supplies will be packaged and labeled in compliance with GMP guidelines. All information regarding study treatment provided will be appropriately documented (ie, batch records, Certificate of Analysis, etc.). The original product packaging will be used in the study (UroGen Pharma Ltd., Israel).

### 7.2.3. Product Storage and Stability

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

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

### 7.2.4. Admixture

The UGN-102 admixture (sterile hydrogel mixed with mitomycin) is stable for 48 hours at 20°C to 25°C (68°F to 77°F), excursion permitted between 15°C and 30°C (59°F and 86°F). Exposure to excessive heat (over 40°C, 104°F) should be avoided. Up to 1 hour before administration, the admixture should be cooled down to between -3°C (27°F) and +5°C (41°F) in order to liquify the UGN-102. The elapsed cooling time must be documented, which includes the length of time at room temperature, as well as length of time in ice.

#### 7.2.5. Product Quality Complaint Handling

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

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

If the PQC is associated with an SAE, the investigational staff must report the PQC to the Sponsor/Sponsor Designee as described above and the SAE(s) must be reported according to Section 9.4.6 (Serious Adverse Event Reporting). The affected study products must be quarantined and marked "not for use" during investigation until a decision has been made regarding the drug's usability.

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.

## 7.3. Study Intervention Compliance

The study treatment will be administered at the investigative site or in the patient's home by properly trained and qualified health care personnel. Each drug administration (including date, time, volume administered) will be documented in the patient's file and eCRF (Section 7.1.3.1).

## 7.4. Dose Modification

Not applicable.

## 7.5. Continued Access to Study Intervention after the End of the Study

No study treatments will be administered to patients after the patient exits from the study.

## 7.6. Treatment of Overdose

Not applicable.

## 7.7. 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 (eg, pharmacological or surgical interventions) related to urothelial carcinoma 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
- Pre-operative non-study chemotherapy

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

The Sponsor Medical Monitor should be contacted if there are any questions regarding prior or concomitant therapy.

### 7.7.1. Rescue Medicine

No rescue therapy is planned for this study.

# 8. Discontinuation of Study Treatment and Patient Discontinuation/Withdrawal

## 8.1. 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 (ie, 3-month Visit). 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.

### 8.1.1. Temporary Withholding of Study Treatment

If at any time during the study the Investigator identifies clinically significant myelosuppression, evidence of an active UTI, or any other significant clinical event or laboratory derangements defined by the parameters below, treatment may be postponed for up to 4 weeks until the clinical event resolves and/or laboratory values improve (Section 9.3.3.1):

- Absolute neutrophil count ≤ 1,000/μL (≥ $1.0\times10^9$/L).
- Platelets ≤ 80,000/μL (≤ $80\times10^9$/L).
- AST/ALT ≥ 5 × ULN.
- Laboratory evidence of active UTI.

### 8.1.2. Rechallenge

No change in dose will be performed for patients who re-initiate their study treatment after temporary withholding (Section 8.1.1).

### 8.1.3. Withdrawal of Consent for Home Instillation of Study Treatment

If the patient withdraws consent for in-home instillation of study treatment, the patient may continue treatment and all scheduled assessments at the investigative site.

## 8.2. 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.

A patient will be considered to have withdrawn from the study for any of the following:

- Withdrawal of consent
- Lost to follow-up
- No longer being followed at the Investigator's discretion
- Protocol non-compliance
- Pregnancy

- Patient experienced an AE that led to study discontinuation
- Death
- Study is closed or terminated by the sponsor

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

At the time of early discontinuation from the study, if possible, an ET Visit should be conducted as shown in the SoA. See Section 1.3 for data to be collected at the time of early discontinuation and for any further evaluations that need to be completed. The patient will be permanently discontinued both from the study treatment and from the study at that time.

## 8.3. Lost to Follow-up

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

# 9. Study Assessments and Procedures

Adherence to the study design requirements, including those specified in the SoA (Section 1.3), 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 (eg, blood count) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

## 9.1. Study Assessments and Procedures by Visit

See the SoA in Section 1.3 for the timing and schedule of all study procedures and assessments.

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

## 9.2. Efficacy Assessments

Efficacy will be assessed at the 3-month Visit.

### 9.2.1. Measurements for Evaluation of Response at 3-month Visit

Assessment of response will be based on the following:

- Visual observation (white light cystoscopy)
- Biopsy of remaining lesions, if applicable (non-complete response [NCR] or suspected tissue)
- Voiding urine cytology

### 9.2.2. Evaluation of Treatment Response at 3-month Visit (Disease Assessment)

Patient response will be evaluated according to the following criteria:

- **CR:** A patient will be considered to have had CR if there is no detectable disease (NDD) at 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 the 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.

- **NCR:** A patient will be considered to have had NCR if there is evidence of 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 are not considered cancer and in such cases the patient would be considered CR.
- **If evidence of disease is identified,** patients will be staged according to the Tumor-Node-Metastases classification and graded according to the 2004 World Health Organization classification of tumors. Any noted progression of tumor in terms of transition to high grade, muscle invasion, distant disease (local assessment) will be documented by the site in the eCRF.
- 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, 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 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.

#### 9.2.3. Pathological Evaluation

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

## 9.3. Safety Assessments

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

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

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

### 9.3.1. Physical Examinations

A full physical examination will be performed at the Screening Visit by a physician at the investigative site. A urological examination will be performed at the Screening Visit, Treatment Visit 1, and at the 3-month Visit (or ET) by a physician at the investigative site. The examinations to be performed are summarized in Table 3. Additional full physical examinations or urological examinations may be performed during the study if clinically indicated.

A clinical assessment will be performed before study drug instillation. Abnormal findings observed at home instillation visits will be documented and reported by the home health professional to the investigative site during the visit.

The patient's height and body weight will be measured during Screening.

**Table 3 Physical Examinations**

| General/Full Physical Examination | Urology-Oriented Physical Examination [a] | Clinical Assessment before study drug instillation |
|---|---|---|
| General appearance | Urethral meatus | General appearance |
| Cardiovascular system | Perineal skin and mucus membranes | Urethral meatus |
| Respiratory system | Scrotum and testes (for male patients) | |
| HEENT (head, eyes, ears, nose, and throat) and neck | Lymphadenopathy | |
| Abdomen | Rectal examination (Screening visit only) | |
| Extremities | Bimanual examination (female patients – Screening visit only) | |
| Neurologic system | | |
| Skin | | |

ET = early termination.
a. Performed before cystoscopy at relevant visits.

### 9.3.2. Vital Signs

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

### 9.3.3. Clinical Safety Laboratory Assessments

Samples for hematology and serum chemistry assessments will be collected according to the SoA in Section 1.3 and tested at the local laboratory. The parameters to be analyzed are listed in Table 4. Other parameters that are part of the local laboratory standard panel may be reported in addition to the protocol-specified parameters.

**Table 4 Laboratory Safety Assessments**

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

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

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

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

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

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

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).

A local laboratory will be used in this study. If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, AE), then the results must be recorded.

#### 9.3.3.1. Other Significant Laboratory Derangements

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

- Absolute neutrophil count ≤ 1,000/µL (≥ $1.0\times10^9$/L)
- Platelets ≤ 80,000/µL (≤ $80\times10^9$/L)
- AST/ALT ≥ 5 × ULN
- Laboratory evidence of active UTI.

### 9.3.4. Urinalysis

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

### 9.3.5. Pregnancy Testing

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

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

## 9.4. AEs, SAEs, and Other Safety Reporting

The definitions of AEs and SAEs can be found in Section 9.4.1.

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

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events as per instructions in Section 9.4.2 and remain responsible for following up all applicable AEs including those that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue the study treatment or from participation in the study (Section 8).

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 9.4.1, Section 9.4.5, and Section 9.4.6.

### 9.4.1. AEs and SAEs

#### 9.4.1.1. Definition of AE

An AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 [a]; 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, serum chemistry, or urinalysis) or other safety assessments (eg, electrocardiogram, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention-intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

**Events <u>NOT</u> Meeting the AE Definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

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

#### 9.4.1.2. Definition of SAE

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

**a. Results in death**

**b. Is life-threatening**

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

**c. Requires inpatient hospitalization or prolongation of existing hospitalization**

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

**d. Results in persistent or significant disability/incapacity**

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

**e. Is a congenital anomaly/birth defect**

**f. Other situations:**

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

#### 9.4.1.3. Classification of an AE

##### *9.4.1.3.1. Severity of Event*

The severity (intensity) of an AE is to be graded by the Investigator according to CTCAE version 5.0 (CTCAE, 2017).

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 (eg, 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).

##### *9.4.1.3.2. Relationship to Study Treatment (Assessment of Causality)*

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

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

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

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

There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor's Designee (via electronic data capture (EDC)/eCRF transmission). However, it is very important that the Investigator always 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.

*9.4.1.3.3. EXPECTEDNESS*

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

An Unexpected Adverse Drug Reaction (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.

### 9.4.2. Time Period and Frequency for Collecting AE and SAE Information

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

Adverse events will be collected from the signing of the ICF until completion of the 3-month Visit (Section 1.3). Information will be captured on the appropriate eCRF including event description, date 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 date of resolution/stabilization of the event. All collected reportable AEs occurring while on study must be documented appropriately. All collected AEs will be followed to adequate resolution/stabilization.

If the study patient's condition deteriorates at any time during the study, it will be recorded as an AE. AEs reported from the time of study treatment administration will be considered as treatment-emergent 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 per the SoA (Section 1.3), the Investigator and/or designee should inquire about the occurrence of AE/SAEs since the last visit. The Investigator or designated investigational staff member should record the start date of all collected reportable events. Events will be followed for outcome information until resolution or stabilization and the dates of outcome must be recorded.

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

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

### 9.4.3. Method of Detecting AEs and SAEs

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

### 9.4.4. Follow-up of AEs and SAEs

After the initial collected AE/SAE report, the Investigator and/or designee is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is provided in Section 9.4.6.

### 9.4.5. Regulatory Reporting Requirements for SAEs

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

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

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

The Investigator must inform the Sponsor/Sponsor Designee about the above by completing and submitting the ***SAE/Death or Pregnancy eCRF*** within 24 hours after its occurrence first came to his/her knowledge.

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

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it

along with the Investigator File and will notify the IRB/IEC, if appropriate according to local requirements.

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

### 9.4.6. 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 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.

#### 9.4.6.1. SAE Reporting Instructions

The Investigator must inform the Sponsor ***within 24 hours*** of becoming aware of an SAE (or updated SAE information) by completing and submitting the ***SAE/Death or Pregnancy eCRF***.

It is not acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor or designee in lieu of completion of the SAE/Death eCRF.

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

If a site receives a report of a new SAE from a study patient or receives updated data on a previously reported SAE when the electronic data capture 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].

### 9.4.7. 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 (Section 9.4.5). 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 (eg, 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 treatment by the Investigator will be reported to the Sponsor as described in Section 9.4.5. While the Investigator is not obligated to actively seek this information in former study patients/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

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

Not applicable.

### 9.4.9. AESIs

In this study, AESIs will be monitored on an ongoing basis through a regular review of adverse event listings. There are no requirements for the Investigator to make determination of AESIs and Investigators are to report all AEs in a consistent manner as described in Section 9.4.2.

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

Current known AESIs include:

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

## 9.5. Pharmacokinetics

Pharmacokinetic and pharmacodynamic parameters are not evaluated in this study.

## 9.6. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

## 9.7. Biomarkers

Biomarkers are not evaluated in this study.

## 9.8. Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

## 9.9. Home Instillation Feasibility Questionnaires

Home instillation feasibility questionnaires will be completed by the patient, the home health professional, and the Investigator at the following time points.

- Patient questionnaire
  - Part 1 must be completed after home instillation of study treatment at Treatment Visits 2 to 6
  - Part 2 must be completed at the 3-month Visit (EOS) or ET Visit
- Home health professional questionnaire
  - Part 1 must be completed after home instillation of study treatment at Treatment Visits 2 to 6
  - Part 2 must be completed after home instillation of study treatment at Treatment Visits 3 to 6
- Investigator questionnaire
  - Must be completed at the 3-month Visit (EOS) or ET Visit

# 10. Statistical Considerations

## 10.1. Statistical Hypotheses

The primary objective of this study is to evaluate the feasibility of home instillation of UGN-102 for treatment of patients with LG IR NMIBC. Analyses are descriptive and exploratory in nature and no formal hypothesis will be tested.

## 10.2. Sample Size Determination

The sample size of this study (approximately 10 patients) is based on feasibility.

## 10.3. Analysis Set

The Safety Analysis Set that includes all patients who received any dose of UGN-102 will serve as the primary population for the analyses of safety and efficacy data in this study.

## 10.4. Statistical Analyses

### 10.4.1. General Considerations

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

### 10.4.2. Primary Endpoint(s)

The primary endpoint is to assess the feasibility of home instillation of UGN-102 by

- Rate of home instillation discontinuations
- Feedback questionnaires from patients, home health professional, and investigator(s)
- Safety profile of UGN-102 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.

**Home Instillation Discontinuations**

Descriptive statistics will be used to summarize proportion of patients discontinuing the home instillations. The frequency and the percentages will be presented.

**Feedback Questionnaire**

Patient questionnaire

Patients will be asked to rate their home instillation experience such as comfort, safety/concerns, communication, preference compared to office instillation and overall experience at each home instillation visit after the instillation is completed. A trend in their responses will be measured descriptively. Patients' home instillation recommendations will also be collected and summarized descriptively at the 3-month Visit/EOS or ET Visit (Appendix A).

Home health professional questionnaire

Home health professionals will also be asked to complete a set of questionnaires after each home instillation visit. Data will be summarized descriptively (Appendix B).

Investigator questionnaire

Investigators will be asked to provide their feedback for each patient based on the experiences of the patient and the home health professional(s) at the 3-month Visit/EOS or ET Visit (Appendix C).

Feasibility of home instillation will be assessed based on the totality of the data.

**Adverse Events**

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

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

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 statistical analysis plan (SAP).

**Clinical Laboratory Data**

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

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

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

Data will be summarized and/or listed separately for hematology, biochemistry, and urinary laboratory tests as appropriate.

**Physical Examination**

Full physical examination will be performed at Screening only. Urology oriented physical examination will be performed at Screening, at the first treatment visit and at the EOS Visit (or ET Visit). Details are provided in Section 1.3 and Section 9.3.1. 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**

Table with descriptive statistics at baseline and post-baseline time points will be summarized. Patients exhibiting clinically notable vital sign abnormalities may be listed.

### 10.4.3. Secondary Efficacy Endpoint(s)

**CR Rate at 3-month Visit (Disease Assessment)**

CR rate is defined as the proportion of patients who achieved CR at the 3-month disease assessment as determined by cystoscopy, for cause biopsy, and urine cytology. If a patient dies or terminates the study prior to the 3-month visit, that patient will be considered as a non-CR and will be included in the denominator to calculate the CR rate. CR rate will be presented along with Exact 95% Clopper-Pearson CIs.

### 10.4.4. Other Analysis

Additional exploratory endpoints may be added in the SAP.

## 10.5. Interim Analysis

No interim analysis will be conducted. The final analysis will be performed after all patients complete the end of study visit or are withdrawn from the study.

# 11. Supporting Documentation and Operational Considerations

## 11.1. Regulatory, Ethical, and Study Oversight Considerations

### 11.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable 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 (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

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 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

### 11.1.2. Finance and Insurance

#### 11.1.2.1. Finance

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

#### 11.1.2.2. Insurance

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

#### 11.1.2.3. 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 requirements, where applicable, and the IRB/IEC or study center.

#### 11.1.2.4. 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 re-screened are required to sign a new ICF.

### 11.1.3. 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 investigative site will permit access to such records.

Patient confidentiality and privacy is strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests 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.

### 11.1.4. Data Review Committee

No data review committee will be implemented for this study.

### 11.1.5. 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.

### 11.1.6. 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.

### 11.1.7. Clinical Monitoring

The Sponsor will perform on-site monitoring visits as frequently as necessary, depending on recruitment frequency at each site. The monitor will record dates of the visits in an investigative site visit log that will be kept at the site. 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 eCRF with the hospital or clinic records (source documents). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and investigational staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

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

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

### 11.1.8. Data Quality Assurance

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

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

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

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

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

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

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

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

### 11.1.9. Data Handling and Record Keeping

#### 11.1.9.1. Data Collection and Management Responsibilities

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

Data collection is the responsibility of the clinical study staff. 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.

Data collected at home health visits will be recorded by the home health professional in the EDC.

#### 11.1.9.2. 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.

### 11.1.10. Protocol Deviations

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

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

### 11.1.11. 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.

### 11.1.12. 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 investigative site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Investigative sites will be closed upon study completion. An investigative site is considered closed when all required documents and study supplies have been collected and an investigative site closure visit has been performed.

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

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

For study termination:

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

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of 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 FDA.

### 11.1.13. 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.

### 11.1.14. 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 A. Patient Questionnaire

The purpose of this questionnaire is for you to share your experience on how you felt receiving UGN-102 intravesical instillation at home. Please indicate the extent to which you felt comfortable and safe with the treatment at home and fill in the questionnaire as per your experience.

**Part 1 Must be completed at each home instillation visit after the instillation is completed**

| | | Not at all | A little | Quite a bit | Very much |
|---|---|---|---|---|---|
| | **Comfort** | | | | |
| 1. | Were you more comfortable with today's instillation at home than at your doctor's office? | | | | |
| 2. | Did you find it more difficult receiving today's instillation at home than at your doctor's office? | | | | |
| | Please explain (free text): | | | | |
| 3. | Did the courtesy and caregiving of the home health professional make you feel comfortable? | | | | |
| | **Safety** | | | | |
| 4. | Did you have any concerns receiving the instillation at home, away from the doctor's office? | | | | |
| | Please explain (free text): | | | | |
| | **Communication** | | | | |
| 5. | Did you receive clear and sufficient instructions on what to do and what to expect before the instillation? | | | | |
| 6. | Did you receive clear and sufficient instructions on what to do and what to expect after the instillation? | | | | |
| | **Preference** | | | | |
| 7. | Did you prefer to have today's instillation done at home compared to the doctor's office? | | | | |
| | Please explain (free text): | | | | |
| | **Overall experience** | | | | |
| 8. | Overall are you satisfied with today's instillation performed at home? | | | | |
| | Please explain (free text): | | | | |

**Part 2 Must be completed at the 3-month Visit (End of Study) or Early Termination Visit**

The purpose of this questionnaire is for you to share your recommendation based on your experience on this study.

1. Will you recommend home instillations of UGN-102 for other patients with non-muscle-invasive bladder cancer (NMIBC)?

   - Yes
   - No

   Please explain (free text):

2. Will you recommend home instillations of UGN-102 instead of having transurethral resection of bladder tumors (TURBT) for other patients with NMIBC?

   - Yes
   - No
   - Not applicable

   Please explain (free text):

## Appendix B. Home Health Professional Questionnaire

The purpose of this questionnaire is for you to share your experience on how you felt administering UGN-102 intravesical instillation at the patient's home. Please indicate the extent to which you felt comfortable and safe with the treatment at the patient's home and fill in the questionnaire as per your experience.

### Part 1 Must be completed at each home instillation visit after the instillation is completed

1. Were you comfortable performing the instillation at this patient's home?
   - Yes
   - No

   Please explain (free text):
2. Was it difficult to perform the instillation at this patient's home?
   - Yes
   - No

   Please explain (free text):
3. Did you have any concerns performing the instillation in the home setting?
   - Yes
   - No

   Please explain (free text):
4. Did you have sufficient support performing the instillation in the home setting?
   - Yes
   - No

   Please explain (free text):

### Part 2 Must be completed starting at the second home instillation visit (Treatment Visit 3 onwards)

1. Did you perform the previous home instillation for this patient?
   - Yes
   - No

## Appendix C. Investigator Questionnaire

**Must be completed at the 3-month Visit (End of Study) or Early Termination Visit**

The purpose of this questionnaire is to understand how comfortable and safe patients and home health professionals considered home instillation of UGN-102. Please answer the questions below.

1. Was the experience of having your patient receive instillations at home more difficult, less difficult, or not different than having them receive instillation in your office?
   - More difficult
   - Less difficult
   - Not different

   Please explain (free text):
2. How can we improve the overall experience (free text)?