A Phase 2b, Single-Arm, Multicenter Trial to Evaluate the Efficacy and Safety of UGN-102 as Primary Chemoablative Therapy in Patients with Low Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk of Recurrence

Protocol Number: TC-BC-12

Sponsor: UroGen Pharma

Country: USA, Israel

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Council on 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 trial patients. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all patient materials will be submitted to the IRB 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 before the changes are implemented to the study. All changes to the consent form will be IRB 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

Title: A Phase 2b, Single-Arm, Multicenter Trial to Evaluate the Efficacy and Safety of UGN-102[1] as Primary Chemoablative Therapy in Patients with Low Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk of Recurrence.

Study Description:

- Trial TC-BC-12 is a prospective Phase 2b single-arm trial to evaluate the efficacy and safety of 6 weekly instillations of UGN-102 in patients with LG NMIBC.
- All enrolled patients will undergo treatment with intravesical UGN-102.
- Approximately 60 patients with LG NMIBC who meet the inclusion/exclusion criteria will be enrolled in the trial.
- Following a successful screening period, eligible patients will be enrolled in the study.
- Eligible patients will receive 6 weekly intravesical instillations of UGN-102. The primary endpoint assessment (complete response [CR]) will take place 5 weeks ±1 week after the last instillation (approximately 3 months after initiation of study treatment), at which time the patients will be evaluated for treatment response.
- Patients who achieve a CR will continue to be monitored monthly for safety, and will be assessed at 6, 9, and 12 months (±2 weeks) after the first instillation of UGN-102 for evidence of disease recurrence. Nonresponders (non-CR) will exit the study and continue with standard of care according to their treating physician.

Objectives:

Primary Objective: To evaluate the tumor ablative effect of UGN-102 in patients with LG NMIBC.

Secondary Objectives:

To evaluate the durability of response in patients with LG NMIBC who achieve CR at the 3 MONTH Visit

To evaluate the safety and tolerability of intravesical UGN-102 instillations in patients with LG NMIBC.

Additional Objective:

To assess the pharmacokinetic profile of Mitomycin C (MMC) in plasma of a subset of patients treated with UGN-102.

Endpoints:

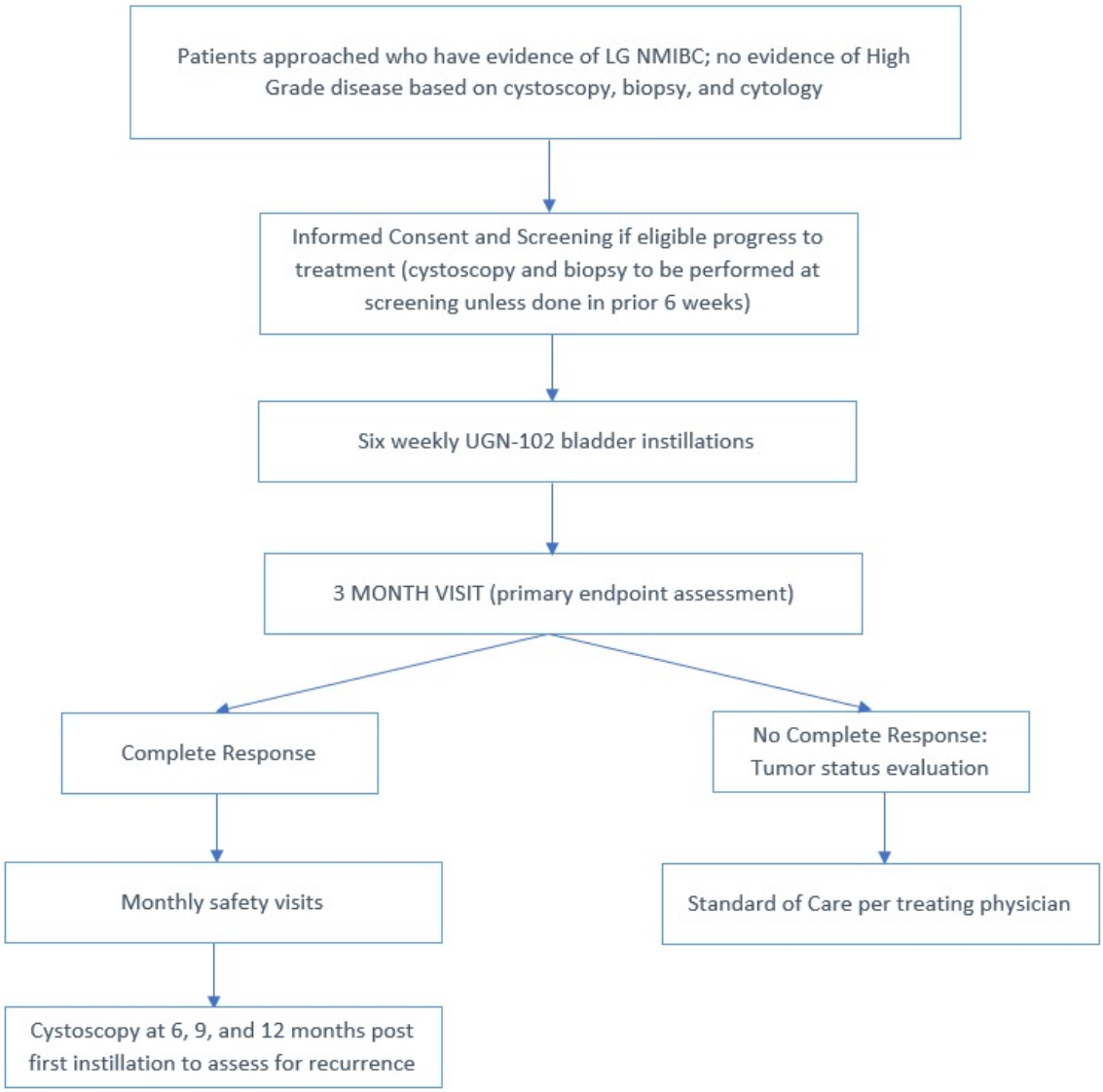
Primary Endpoint: CR rate for UGN-102 treatment in patients with LG NMIBC at the 3 MONTH Visit (3 months after the first instillation of UGN-102) as assessed by cystoscopy, with or without biopsy, and urine cytology.

Secondary Endpoints:

[1] UGN-102 was formerly known as VesiGel.

	Efficacy: Durable complete response (DCR) rate: proportion of patients with no evidence of disease at 6, 9, and 12 months after the first instillation of UGN-102 in patients who achieved CR at the 3 MONTH Visit. **Safety:** Frequency, severity, and types of adverse events (AEs), including AEs of special interest; changes from baseline in laboratory values and incidence of measurements defined as potentially clinically significant; and clinically meaningful changes in physical examination findings. **Tertiary/Exploratory Endpoints:** **Pharmacokinetic:** The pharmacokinetic (PK) profile of the first MMC instillation in the blood will be examined in a subset of six patients. **Quality of Life (QoL):** To examine patient reported outcome of health-related quality of life
Study Population:	Patients who have been diagnosed with LG NMIBC, and determined to have intermediate risk of recurrence, defined as 1 or 2 of the following: multiple tumors, solitary tumor >3 cm, or recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis).
Phase:	Phase 2b
Description of Sites/Facilities Enrolling Patients:	This study will be conducted by appropriately trained urologists at approximately 30 sites in North America and Israel.
Description of Study Medication:	UGN-102 preparation for intravesical instillations, containing Mitomycin C (MMC) 80 mg and 60 mL UG-1 gel, in order to administer 75 mg MMC in a 56 mL instillation (1.33 mg mitomycin per mL). Treatment duration: 6 instillations, administered once weekly over 6 weeks.
Study Duration:	Approximately 26 months (from first center initiated [FCI] until last patient last visit [LPLV]).
Patient Duration:	Approximately 13 months per patient (from enrollment through last visit).

1.2 Schema



LG = low grade; NMIBC = non-muscle-invasive bladder cancer

1.3 Schedule of Activities (SoA)

1.3.1 Screening to 3 MONTH Visit

Procedures	Screening Day -14 to Day -1 or Day -28 to Day -1[§]	Enrollment and Baseline Study Visit 1 Day 1	Study Visit 2 Day 8 -1/ +3 days*	Study Visit 3 Day 15 -1/ +3 days *	Study Visit 4 Day 22 -1/ +3 days *	Study Visit 5 Day 29 -1/ +3 days *	Study Visit 6 Day 36 -1/ +3 days *	3 MONTH Study Visit 7 5 weeks ±1 week after last instillation (3 months post initiation)[†]	Unscheduled Visit^
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics	X								
Medical history	X								
Administer study medication		X	X	X	X	X	X		
Concomitant medication review	X	X	X	X	X	X	X	X	X
Directed physical examination[‡]	X	X			X			X	
Vital signs	X	X	X	X	X	X	X	X	X
Height	X								
Weight	X	X		X		X		X	
Hematology	X	X	X	X	X	X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X
Urinalysis[#]	X	X	X	X	X	X	X	X	X
Pregnancy test	X							X	
Administer QLQ – NMIBC24		X						X	X
PK (in a subset of 6 patients)		X							
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X
Cystoscopy/urine cytology***	X							X***	X
Cold cup biopsy****	X								
CT Urogram*****	X								
Complete eCRFs	X	X	X	X	X	X	X	X	X

[§] The screening period is up to 14 days for patients that do not need a screening biopsy and up to 28 days for patients that need a screening biopsy (see sect. 10.1.1)
3 MONTH = Primary endpoint assessment; CT; eCRF =; Non-CR = nonresponder.
* Windows are provided to accommodate patient logistics in scheduling. In any case, instillations should not occur more frequently than 6 days apart.
[†] Patients who discontinue before the 3 MONTH Visit or who are discontinued as Non-CR at the MONTH 3 Visit should have all assessments specified for the 3 MONTH Visit as their end-of-study assessments. Patients discontinued as Non-CR will be managed according to best practice according to their treating physician (refer to Section 10.2.2).
^ If an unscheduled visit is required, assessments should be performed as appropriate to the needs of the visit, although safety assessments should be performed, if feasible.
‡ Full physical examination at Screening; urology-oriented physical examination at Visits 1, 4, and 7 (Refer to Section 10.5.4: Table 5).
[#]To include culture and sensitivity at Screening.
** No cytology needed if results from a prior cytology within 6 weeks of screening are available)
*** Biopsies may be needed at 3 months if any remaining lesions are visualized during cystoscopy (Sect.10.2.1, 10.2.2)
**** Cold cup biopsy to confirm LG performed only if not already performed within 6 weeks of screening
***** Acceptable if performed within 6 months prior to Screening

1.3.2 *Complete Responder at 3 MONTH Visit: Visit 8 to End of Study*

Procedures	Telephone Visit 8 4 months post initiation ±1 week	Telephone Visit 9 5 months post initiation ±1 week	Study Visit 10 6 months post initiation ±2 weeks	Telephone Visit 11 7 months post initiation ±1 week	Telephone Visit 12 8 months post initiation ±1 week	Study Visit 13 9 months post initiation ±2 weeks	Telephone Visit 14 10 months post initiation ±1 week	Telephone Visit 15 11 months post initiation ±1 week	END OF STUDY Study Visit 16 12 months post initiation ±2 weeks	Unscheduled Visit^
Concomitant medication review	X	X	X	X	X	X	X	X	X	X
Full physical examination									X	
Vital signs			X			X			X	X
Weight						X				
Hematology			X			X			X	X
Serum chemistry			X			X			X	X
Urinalysis			X			X			X	X
Pregnancy test										
Administer QLQ - NMIBC24			X			X			X	X
Adverse event review and evaluation	X	X	X	X	X	X	X	X	X	X
Cystoscopy/urine cytology§			X			X			X	X
Complete eCRFs	X	X	X	X	X	X	X	X	X	X

^ If an unscheduled visit is required, assessments should be performed as appropriate to the needs of the visit, although safety assessments should be performed, if feasible.

§ Any patient with evidence of disease recurrence post-CR will be documented as such, discontinued from the study, and should have all assessments specified for the END OF STUDY Visit as their end-of-study assessments. Patients discontinued with disease recurrence will be managed according to best practice according to their treating physician Refer to Section 10.2.4.

2 ABBREVIATIONS

3 MONTH	3 Month Visit
3 MONTH$_{CR}$	Complete Response at 3 MONTH Visit
ADL	Activities of daily living
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BCG	Bacille de Calmette et Guérin
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CIS	Carcinoma in situ
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Durable complete response
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
FCI	First center initiated
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HG	High grade
HRQoL	Health Related Quality of Life
ICF	Informed Consent form
ICH	International Council on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug
IP	Investigational Product
IQR	Interquartile range
IRB	Institutional Review Board
ITT	Intent-to-Treat
LG	Low grade
LPLV	Last patient last visit
LUTS	Lower urinary tract symptoms

MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMC	Mitomycin C
NCI	National Cancer Institute
NDD	No detectable disease
NMIBC	Non-muscle-invasive bladder cancer
non-CR	Nonresponders
PCS	Potentially clinically significant
PI	Principal Investigator
PK	Pharmacokinetics
PP	Per Protocol
PQC	Product Quality Complaint
PT	Preferred Term
PUNLMP	Papillary Urothelial Neoplasm of Low Malignant Potential
QLQ	Quality of Life Questionnaire
QC	Quality control
SAE	Serious adverse event
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SMP	Study Monitoring Plan
SoA	Schedule of Activities
SoC	Standard of care
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
ST	Safety
TEAE	Treatment-emergent adverse event
TNM	Tumor Node Metastases
TURBT	Transurethral resection of bladder tumor
UADR	Unexpected Adverse Drug Reaction
UC	Urothelial carcinoma/cancer
UG-1	UG-1 Sterile Hydrogel by UroGen Pharma Ltd.
UGN-102	UGN-102 preparation of UG-1 hydrogel mixed with mitomycin C, using the kit components
US	United States
USP	United States Pharmacopeia
UTI	Urinary tract infection
UTUC	Upper tract urothelial carcinoma
WHO	World Health Organization

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4 INTRODUCTION

4.1 Study Rationale

Non-Muscle-Invasive Bladder Cancer

Urothelial cancer (UC) of the bladder is the second most common genitourinary malignancy, with almost 80,000 new cases diagnosed annually in the United States (US) and nearly 17,000 deaths from the disease per year. Non-muscle-invasive bladder cancer (NMIBC) accounts for about 80% of all bladder cancers (Heney, 1992). Patients with NMIBC can be segmented into 3 staging groups: patients with Ta tumors (70%), patients with T1 tumors (20%), and patients with carcinoma in situ (CIS) or Tis tumors (10%). Of these patients, approximately 70% have a tumor that is classified as low grade (LG), and approximately 30% have a tumor that is classified as high grade (HG). Ta and CIS tumors are limited to the urothelial layer, and T1 is limited to the lamina propria.

The standard treatment of NMIBC is transurethral resection of bladder tumor (TURBT) (Brausi, 2002), often followed by adjuvant intravesical chemotherapy or immunotherapy (Hall, 2007). TURBT is associated with the typical risks of surgery including injury to the bladder and postoperative bleeding. Recurrence rates following standard of care (SoC) management range from 31% to 78% with the risk of progression to muscle invasion approaching 50% in patients with HG cancer (Sylvester, 2006). Tumor recurrence following TURBT can be attributed primarily to incomplete initial resection and, at least hypothetically, to tumor cell reimplantation following surgery (Brausi, 2002; Miladi, 2003, Anastasiadis, 2012). The effectiveness of intravesical therapy is limited by urine production, which results in drug dilution and periodic bladder emptying, and which limits the agent's time on target (Audenet, 2013; Barlogie, 1980; De Bruijn, 1992; Deb, 2011; Eastham, 1993; Nozue, 1995a; Ozawa, 1988; Perry, 1992; Sadeghi, 1998; Schmittgen, 1991; Slee, 1986; Walker, 1986; Wang, 2013, O'Donoghue, 2004).

Chemoablation represents an attractive alternative to surgical therapy. It could avoid the morbidity and expense of surgery and may offer a more rational therapeutic approach to UC, which is generally multifocal and refractory to focal ablative interventions. Preliminary evidence documents the ablative capabilities of aqueous Mitomycin C (MMC), which has been applied successfully to the primary management of small UCs (Bono, 1996; Bracken, 1980; Brausi, 1998; Colombo, 2001; Ost, 2015; Hamdy, 1993; Harrison, 1983; Hetherington, 1987; Maffezzini, 1996; Mishina, 1975; Soloway, 1985.)

UGN-102

The Sponsor performed a Phase 2 study (Study TAS-4M-CS-002) in 65 evaluable patients with LG NMIBC and showed that UGN-102 therapy is associated with a complete response (CR) rate of 86% and significant durability of response (77% recurrence free survival at 12 months) in those patients achieving an initial CR. Based on this initial experience, the Sponsor proposes to conduct a Phase 2b UGN-102 trial in the US to corroborate the data provided by the European Trial.

Study TC-BC-12

This study is a prospective, Phase 2b, single-arm, open-label trial to evaluate the efficacy and safety of UGN-102 75 mg given once weekly intravesically, for a total of 6 doses, in the treatment of patients with LG NMIBC at intermediate risk of recurrence.

4.2 Background

UGN-102 is a reverse thermal hydrogel formulated with MMC. The product is specifically formulated to achieve a liquid state at 4°C and to transition to a water-soluble gel at body temperature. The advantage of delivering Mitomycin to the urinary bladder using UGN-102 relies on preclinical and clinical literature documenting that concentration and dwell time correlate directly with the therapeutic efficacy of MMC when used to treat UC (Barlogie, 1980; Slee, 1986; Walker, 1986; Ozawa, 1988; Perry, 1992; Nozue, 1995b; Sadeghi, 1998).

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

UGN-102 Investigational Product

UGN-102 is provided by UroGen Pharma as a kit containing 2 vials of 40 mg MMC for injection, one 60 mL vial of UG-1 (UG-1 sterile hydrogel), 3 × 30 mL sterile syringes, and sterile syringe stoppers. The proprietary hydrogel, UG-1, allows for a sustained release of MMC at the target site of administration, resulting in prolonged exposure of the tumor cells to MMC, where it can exert a chemical ablative effect.

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

For further details of the preclinical and clinical studies conducted with UGN-102, refer to the Investigator Brochure for UGN-101 (MitoGel) and UGN-102 (VesiGel).

4.3 Risk/Benefit Assessment

4.3.1 Known Potential Risks

Toxicity Associated with Systemic Absorption/Local Irritation

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

Allergic Response to MMC

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

Cystitis

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

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

Currently, the SoC for NMIBC is TURBT. This surgical procedure has its own potential risks such as bladder perforation resulting in MMC leak, bladder scarring, and decreased bladder capacity; urinary retention requiring catheterization; and the need for anesthesia. Moreover, during TURBT, tumor cells are released into the bladder cavity and may be seeded in denuded areas of the bladder where the urothelium is surgically interrupted. This is one of the reasons for the high rate of tumor recurrence and the need of immediate post-TURBT chemotherapy (usually MMC instillations). The high recurrence rate of NMIBC indicates that the current SoC is far from optimal.

4.3.2 Known Potential Benefits

The potential advantages of instillation of MMC in gel are as follows:

- Sustained release of drug for up to 8 hours (compared with 1.5 to 2 hours in standard instillation). Published literature indicates that duration of tumor exposure to chemotherapy is critical to its ablative response. Thus, the effectiveness of tumor ablation is increased by longer dwell times.
- The gel protects MMC from both breaking down in urine and being diluted by urine, which leads to longer stable chemotherapy concentration levels.

These characteristics of UGN-102 (MMC+UG-1) are expected to improve MMC treatment efficacy and provide an alternative mode of ablation for NMIBC, which may be simpler and potentially better tolerated than current treatment modalities.

4.3.3 Assessment of Potential Risks and Benefits

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

5 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To evaluate the tumor ablative effect of UGN-102 in patients with LG NMIBC	CR rate for UGN-102 treatment in patients with LG NMIBC at the 3 MONTH Visit (3 months after the first instillation of UGN-102) as assessed by cystoscopy, with or without biopsy, and urine cytology	Consistent with clinical practice for disease response to intervention. Regulatory guidance.
Secondary		
To evaluate the durability of response in patients with LG NMIBC who achieve CR at the 3 MONTH Visit	Durable complete response (DCR) rate: proportion of patients with no evidence of disease at 6, 9, and 12 months after the first instillation of UGN-102 in patients who achieved CR at the 3 MONTH Visit	Consistent with clinical practice for disease response to intervention. Regulatory guidance.
To evaluate the safety and tolerability of intravesical UGN-102 instillations in patients with LG NMIBC	Frequency, severity, and type of adverse events (AEs), including adverse events of special interest (AESIs), changes from baseline in laboratory values and incidence of measurements defined as Potentially Clinically Significant (PCS); and clinically meaningful changes in physical examination findings	Standard endpoints for safety evaluation in the patient population.
Tertiary/Exploratory		
To assess the pharmacokinetic (PK) profile of the first MMC instillation in six (6) patients	Concentration data as well as PK parameters (e.g., AUC, $C_{max,}$ etc.)	To evaluate the PK profile of intravesicular UGN-102 in order to understand the risk of systemic mitomycin exposure
To examine patient reported outcome of health-related quality of life as compared to baseline	QLQ - NMIBC24 at 3, 6, 9, 12 months or ET	Exploratory

6 STUDY DESIGN

6.1 Overall Design

This study is a prospective, proof of concept, open-label, single-arm, multicenter Phase 2b trial designed to assess the efficacy and safety of UGN-102 treatment instilled in patients diagnosed with LG NMIBC including newly-diagnosed patients, and determined to have intermediate risk of progression, defined as 1 or 2 of the following: multiple tumors, tumors >3 cm, or recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis). Eligible patients will be treated with 6 weekly instillations of UGN-102.

Upon signing of informed consent, patients will undergo a Screening Visit for eligibility evaluation. The screening period is 2 weeks if the patient's cold cup biopsy to confirm LG tumor is historic (taken within 6 weeks of the screening visit) or 4 weeks if the patient's cold cup biopsy to confirm LG tumor is current (taken at the screening visit).

Starting at the Baseline Visit (Day 1), eligible patients will be treated with UGN-102 once weekly for a total of 6 doses; the UGN-102 concentration to be used in this trial will be 1.33 mg MMC per 1mL. The volume of UGN-102 to be instilled will be 56 mL (75 mg of MMC).

The ablative effect of UGN-102 will be evaluated at the 3-month assessment, which will take place 5 weeks ±1 week after the last weekly instillation (3 months after initiation of study medication). Response will be determined based on visual evaluation by cystoscopy (appearance, number, and size of the lesions) and, if there are remaining lesions, by histopathology of the remaining lesions. CR is defined as having no detectable disease (NDD) and will be assessed visually during cystoscopy and also upon urine cytology. In the event that the investigator is not sure, and there is suspect tissue, a small biopsy will be taken from the suspect tissue to confirm CR in addition to cystoscopy and urine cytology. Patients who achieve a CR will continue to have monthly telephone contacts to document any adverse events and changes in concomitant medications and will be assessed at 6, 9, and 12 months after the first instillation of UGN-102 for evidence of disease recurrence. The group of patients considered nonresponders (non-CR) will discontinue the study and continue with SoC according to their treating physician.

Safety will be determined based on physical examination, laboratory assessments, and a review of AEs. All safety data will be reviewed on an ongoing basis, including close review and follow up of any unexpected AE related to UGN-102 and qualified per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) as Grade 3 or 4.

6.2 Scientific Rationale for Study Design

The single-arm, noncomparative design was chosen to confirm the results of a previous study (Study TAS-4M-CS-002), which indicated that a dose regimen of 6 weekly instillations of UGN-102 75 mg was effective and well tolerated in patients with LG NMIBC. Based on data from an ongoing Phase 3 trial in a similar indication, UTUC, monthly maintenance treatments do not appear to have a meaningful effect on durability of response in those patients who were CR at the 3-month assessment (primary endpoint). This study also aims to treat a slightly more challenging population: those at increased risk for recurrence.

6.3 Justification for Dose

The UGN-102 dose of 75 mg was chosen based on both efficacy and tolerability.
Study TAS-4M-CS-002 demonstrated numerically higher CR rates for the 75 mg dose than for the 37.5 mg dose. In Study TC-BC-10, 120 mg of UGN-102 had a similar response rate to 75 mg and a higher rate of AEs.

Although this is a single-arm, noncomparative study, patients who do not achieve CR after 6 weekly instillations of UGN-102 75 mg will exit the study and be treated according to best practice according to their treating physician.

6.4 End of Study Definition

A patient is considered to have completed the study when he or she has completed all phases of the study, including the last visit or the last scheduled procedure and assessment according to the Schedule of Activities (SoA), Section 1.3.

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

7 STUDY POPULATION

7.1 Inclusion Criteria

In order to be eligible to participate in this study, a patient must meet all of the following criteria:

1. ≥ 18 years of age.
2. Willing and able to sign an informed consent and comply with the protocol.
3. Has newly diagnosed or historic LG NMIBC (Ta) histologically confirmed by cold cup biopsy at screening or within 6 weeks of screening.
4. Is at intermediate risk for progression, defined as having 1 or 2 of the following:
    a. presence of multiple tumors,
    b. solitary tumor >3 cm
    c. recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis).
5. Has negative voiding cytology for HG disease at or within 6 weeks of enrollment.
6. Willing to use 2 acceptable forms of effective contraception from enrollment through 6 months post treatment if the participant is female or the female partner of a male participant is of childbearing potential (defined as premenopausal women who have not been sterilized).
7. Has adequate organ and bone marrow function as determined by routine laboratory tests as below:
    - Leukocytes ≥3,000/µL (≥3×10^9/L),
    - Absolute neutrophil count ≥1,500/µL (≥1.5×10^9/L),
    - Platelets ≥100,000/µL (≥100×10^9/L),
    - Hemoglobin ≥9.0 mg/dL,
    - Total bilirubin ≤1.5 upper limit of normal (ULN),
    - AST (SGOT)/ALT (SGPT) ≤2.5 × upper limit of normal (ULN),
    - ALP ≤2.5 × ULN, and
    - Estimated glomerular filtration rate (eGFR) ≥30 mL/min.

8. Has no evidence of active urinary tract infection* (UTI) at Screening and Baseline visits.

**In the case of symptomatic UTI, the patient will be treated with a full course of antibiotics, and study medication will be postponed until resolution. In the case of asymptomatic bacteriuria, the use of prophylactic antibiotics and postponement of study medication is left to the discretion of the Principal Investigator (PI).*

7.2 Exclusion Criteria

A patient who meets any of the following criteria will be excluded from participation in this study:

1. History of CIS on preliminary cystoscopy within 5 years of enrollment.
2. Received BCG treatment for UC within previous 2 years.
3. History of HG papillary UC in the past 2 years
4. Known allergy or sensitivity to mitomycin.
5. Clinically significant urethral stricture that would preclude passage of a urethral catheter.
6. History of pelvic radiotherapy.
7. History of:
   a) neurogenic bladder
   b) active urinary retention
   c) any other condition that would prohibit normal voiding
8. Past or current muscle invasive (i.e., T2, T3, T4) or metastatic UC or concurrent upper tract urothelial carcinoma (UTUC).
9. Has participated in a study with an investigational agent or device within 30 days of enrollment.
10. History of prior treatment with an intravesical chemotherapeutic agent with the exception of a single dose of chemotherapy immediately post any previous TURBT
11. Has an underlying substance abuse or psychiatric disorder such that, in the opinion of the investigator, the patient would be unable to comply with the protocol.

7.3 Lifestyle Considerations

Not applicable.

7.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, eligibility criteria, and any serious adverse event (SAE).

7.5 Strategies for Recruitment and Retention

Approximately 66 patients will be screened and recruited to ensure that approximately 60 patients with LG NMIBC who meet the eligibility criteria complete the study (assuming a 10% dropout rate). The study will be conducted primarily by appropriately trained urologists at approximately 20 to 30 study sites in North America and Israel who provide care to patients with bladder cancer.

8 STUDY MEDICATION

8.1 Study Medication Administration

8.1.1 Study Medication Description

The UGN-102 preparation for intravesical instillations contains MMC 75 mg in 56 mL admixture (1.33 mg MMC per 1 mL of admixture). UGN-102 admixture is prepared in advance of use by the pharmacy, up to 48 hours before administration (this time is supported by in-use stability data of at least 48 hours). The UGN-102 Kit contains 4 components (Table 1):

Table 1 UGN-102 Kit Components

Component	Quantity (per kit) †	Function
Mitomycin for Injection, USP (vial)	2 × 40-mg	Active Ingredient
UG-1 Sterile Hydrogel (vial)	1 × 60 mL	Vehicle
Labels	7	Preparation labels
Preparation Leaflet	1	Instructions for preparation

† For the proposed indication, each 40 mg MMC will be mixed with 3 mL sterile WFI and 27 mL UG-1 sterile hydrogel. A total of 56 mL of the 1.33 mg/mL preparation will be instilled in each patient. The gel and MMC excess included in the kit are to allow for the required UGN-102 volume withdrawal from the vials.
MMC = Mitomycin C; USP = United States Pharmacopeia; WFI = water for injection.

The vials of 40 mg MMC for injection are manufactured for UroGen Pharma Ltd, 9 Ha'Ta'asiya Street, Ra'anana, Israel, by Cenexi-Laboratoires Thissen, S.A. rue de la Papyrée 2-4-6, B-1420 Braine-l'Alleud, Belgium. MMC is provided as a dry lyophilized powder in 100 mL vials and will be stored at 15°C to 30°C.

The contents of each MMC for injection United States Pharmacopeia (USP) vial are listed in Table 2.

Table 2 Vial Composition of Mitomycin for Injection, USP

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

USP = United States Pharmacopeia.

The 60 mL vials of UG-1 sterile hydrogel are manufactured for UroGen Pharma Ltd, 9 Ha'Ta'asiya Street, Ra'anana, Israel, by Isorad Ltd., P.O. Box 239, Yavne, 8110102, Israel. UG-1 sterile hydrogel is provided in a 100-mL glass vial and will be stored at 15°C to 30°C.

The contents of each UG-1 sterile hydrogel vial are a proprietary blend of Poloxamer 407, hydroxypropyl methyl cellulose, polyethylene glycol (molecular weight 400), and water for injection.

The components of the UGN-102 Kit are produced under aseptic conditions and according to current Good Manufacturing Practice (GMP) (European Commission, May 2003 Guidelines). The UGN-102 Kit lots to be used in this trial are tested and released under supervision and approval by the UroGen Quality Assurance Department.

8.1.2 Preparation and Administration Ancillary Supplies and Devices

All ancillary supplies and devices used to prepare and administer the study medication are detailed in the Instructions for Use (IFP) and Instructions for Pharmacy (IFP) Document Numbers: IFU-Phy0002696) and IFP (IFP-0002643).

8.1.3 Dosing and Administration

The patients entering this trial will undergo 6 weekly instillations of UGN-102.

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

* Refer to UroGen's Injector Device Instructions for Use Manual for detailed instillation instructions.

The UGN-102 preparation will be administered for therapy in the bladder as 6 weekly, consecutive instillations, at Study Visits 1, 2, 3, 4, 5, and 6. Study drug administration will be documented in the patient file, electronic Case Report Forms (eCRFs), and in the Drug Administration Records.

8.2 Preparation/Handling/Storage/Accountability

8.2.1 Acquisition and Accountability

The UGN-102 Kit assembled for UroGen Pharma Ltd. 9 Ha'Ta'asiya St., Ra'anana, Israel by CSM Europe sa, Watson & Crick Hill, Rue Granbonpré 11 | B-1435 Mont-Saint-Guibert, Belgium, will be provided by the Sponsor. All clinical supplies will be packaged and labeled in compliance with GMP guidelines. The shipment process should comply with the rules of Good Distribution Practices. Prior to shipment of clinical supplies, the Sponsor must notify the PI regarding the anticipated date of arrival at the hospital/clinic pharmacy. The investigational product (IP) will be sent to the site only after trial approval by the Institutional Review Board (IRB) has been received. The shipment will be sent to the investigator's authorized trial personnel at the site's pharmacy.

All trial medications dispensed will be appropriately documented to ensure proper handling in case of emergency.

The Sponsor will ship all drugs to the pharmacy/approved designee at a controlled room temperature between 15°C and 30°C. 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 the Sponsor's Quality

Assurance Group by email (qa@urogen.com) immediately and complete the product quality complaint (PQC) form (see Section 8.2.5). 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 trial 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 Kits must be available for verification by the sponsor’s site monitor during on-site monitoring visits. Unused or expired UGN-102 Kits returned to the Sponsor must be documented on the drug return form.

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

Unusable UGN-102 Kits will be marked “not for use” in pen over the label and stored separately from usable UGN-102 Kits.

Replacement UGN-102 Kits will be supplied after request for additional kits has been issued to the Sponsor, the distributor for the trial, or the US depot.

Following completion of drug accountability by the CRA, used trial drug vials should be discarded locally according to local institution guidelines for cytotoxic waste destruction. Discarding of the used UGN-102 preparation vials must be documented in the drug disposal form.

8.2.2 Formulation, Appearance, Packaging, and Labeling

The formulation of the study medication and the contents of the UGN-102 Kit are described in Section 8.1.1. All clinical supplies will be packaged and labeled in compliance with GMP guidelines. All information regarding trial medications provided will be appropriately documented (i.e., batch records, Certificate of Analysis, etc.). The original product packaging will be used in the trial (UroGen Pharma Ltd., Israel).

The kit will be labeled as follows:

Caution: New Drug-Limited by Federal (or United States) law to investigational use

UGN-102 Kit for Urologic Use

Protocol: TC-BC-12

Each kit contains:

Quantity per Kit	Component
2 vials	Mitomycin for Injection, USP, 40 mg
1 vial	UG-1 Sterile Hydrogel, 60 mL
7	Labels
1	Instructions for Pharmacy

Storage: Retain the vials in the carton until use. Store the kit at 25°C (77°F), excursion permitted between 15°C (59°F) and 30°C (86°F). Avoid excessive heat (over 40°C or 104°F).

Use the Instructions for Pharmacy leaflet while preparing the UGN-102 Admixture.

UroGen Pharma Ltd. 9 Ha'Ta'asiya St., Ra'anana, Israel. Tel: +972-9-770-7600
Packed by: CSM Europe SA, Watson & Crick Hill, Rue-Granbonpré 11, B-1435 Mont-Saint-Guibert, Belgium. Tel: +32-10-237444

Kit Batch Number: Mfg Date:
Kit serial Number:

8.2.3 Product Storage and Stability

The UGN-102 Kit must be stored at a controlled room temperature of 25°C (77°F), excursion permitted between 15°C (59°F) and 30°C (86°F). Avoid excessive heat (over 40°C or 104°F) in accordance with applicable regulatory requirements for cytotoxic substances.

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

8.2.4 Preparation

The UGN-102 preparation (UG-1 gel mixed with MMC) is stable for 48 hours at 25°C (77°F), with variation permitted between 15°C (59°F) and 30°C (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 and +5°C in order to liquify the UGN-102. The elapsed cooling time must be documented from the point the mixture is prepared until it is instilled, which includes the length of time at room temperature, as well as length of time at a refrigerated temperature.

8.2.5 Product Quality Complaint Handling

A Product Quality Complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging; i.e., any dissatisfaction relative to the identity, quality,

durability, or reliability of a product, including its labeling or packaging integrity. In such cases, and also in cases of temperature deviation, either during transport or storage at the pharmacy, the investigator is responsible for notifying the Sponsor in writing using the PQC form about the defect/temperature deviation. Any written PQC report must be reported to the Sponsor by email to: qa@urogen.com.

ATTN: Quality Assurance

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

If the defect is combined with an SAE, the investigational staff must report the PQC to the Sponsor according to the SAE reporting timelines (refer to Section 10.4.6; Serious Adverse Event Reporting). The affected trial 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.

8.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable; this is an open-label, single-arm study.

8.4 Study Medication Compliance

The study medication will be administered at specified treatment visits by properly trained study site staff members. Each drug administration will be documented in the patient's file and eCRF.

8.5 Concomitant and Prohibited Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications, and supplements. Prohibited concomitant medications include systemic chemotherapy, intravesical chemotherapy, and immunotherapy for bladder cancer treatment including but not limited to BCG.

In cases of symptomatic UTI, the patient will be treated with a full course of antibiotics, and study medication will be postponed until resolution. In the case of asymptomatic bacteriuria, the use of prophylactic antibiotics and postponement of study medication is left to the discretion of the Principal Investigator (PI).

8.5.1 Rescue Medicine

Patients considered non-CR at the 3 MONTH Visit (Visit 7) will exit the study and will be treated according to best practice according to their treating physician.

9 STUDY MEDICATION DISCONTINUATION AND PATIENT DISCONTINUATION/WITHDRAWAL

9.1 Discontinuation of Study Medication

Discontinuation from study medication does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to, changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in patient management is needed. Any new clinically relevant finding will be reported as an AE.

If a patient discontinues study medication during the treatment period or at any time prior to the 3 MONTH Visit, the following unscheduled visit activities should be performed:

- All 3 MONTH Visit (Visit 7) procedures should be conducted.
- If the patient appears to have a CR (refer to Section 10.2.2), the patient has the option to continue participating in the follow-up assessments conducted at Months 6, 9, and 12 (Visits 10, 13, and 16, respectively) to assess for disease recurrence and monthly telephone contacts for safety checks.
- If patient agrees to complete the follow-up visits within the trial or agrees to continue to share information regarding his/her disease status, information collected during the follow-up care of the patient should be recorded in the eCRF.

9.2 Patient Discontinuation/Withdrawal from the Study

Patients in this trial are free to withdraw from participation in the study at any time.

An investigator may discontinue or withdraw a patient from the study for the following reasons:

- Pregnancy
- Significant study medication non-compliance
- If any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the patient
- Disease progression that requires discontinuation of the study medication
- If the patient meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation
- Patient becomes unable to receive study medication for 4 weeks.
- Patient is lost to follow-up (see section 9.3)

The reason for patient discontinuation or withdrawal from the study will be recorded on the eCRF. Patients who sign the informed consent form but do not receive the study medication may be replaced. Patients who sign the informed consent form, receive the study medication, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

9.3 Lost to Follow-Up

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

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

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

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

10 STUDY ASSESSMENTS AND PROCEDURES

10.1 Study Assessments and Procedures by Visit

10.1.1 Screening Period (Day -28 to Day -1 or Day -14 to Day -1)

For patients that need a biopsy, the screening period is up to 28 days. For patients that do not need a biopsy, the screening period is up to 14 days. The following procedures will be performed at Screening:

- Obtain written informed consent before any study-related procedures are performed
- Inclusion and exclusion criteria
- Demographics
- Medical history
- Concomitant medication review
- Full physical examination (including height and weight) and urology-oriented physical examination
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature)
- Clinical laboratory tests (serum chemistry and hematology)
- Urinalysis (dipstick on-site and culture and sensitivity at local lab)
- Urine pregnancy test (if appropriate)
- Cystoscopy and urine cytology (if not performed within 6 weeks of screening)
- Collection of a single representative cold cup biopsy, if no histologic confirmation of LG tumor within 6 weeks of screening
- Computerized tomography (CT) Urogram, retrograde pyelogram, or MRI (if other tests are contraindicated) to rule out UTUC (acceptable if performed within 6 months of Screening)

- AE review

10.1.2 ***Enrollment and Baseline Visit (Visit 1, Day 1)***

The following procedures will be performed at Visit 1:

- Administer QLQ-NMIBC24 questionnaire
- Concomitant medication review
- Urology-oriented physical examination
- Body weight
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature)
- Clinical laboratory tests (serum chemistry and hematology)
- Urinalysis
- Blood collection for PK at select sites in 6 patients at 0 hr. pre-instillation and 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, and 6.0 hrs. post instillation
- AE review
- Confirm all inclusion and exclusion criteria are met
- Administer study medication*
- Keep patient in clinic for 30 to 60 minutes post instillation

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

10.1.3 ***Visits 2*, 3*, 4*, 5*, and 6* (Days 8*, 15*, 22*, 29*, and 36*)***

** -1+ 3 days. Windows are provided to accommodate patient logistics in scheduling. Instillations should not occur more frequently than 6 days apart.*

The following procedures will be performed at Visit 2 (Day 8) through Visit 6 (Day 36):

- Concomitant medication review
- Urology-oriented physical examination (Visit 4 only)
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature)
- Body weight (Visits 3 and 5 only)
- Clinical laboratory tests (serum chemistry and hematology)
- Urinalysis
- AE review
- Administer study medication

10.1.4 ***Visit 7 (Month 3 ± 1 week)***

The following procedures will be performed at Visit 7 (Month 3):

- Administer QLQ-NMIBC24 questionnaire
- Concomitant medication review
- Urology-oriented physical examination
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature)
- Body weight
- Clinical laboratory tests (serum chemistry and hematology)
- Urinalysis
- Urine pregnancy test (if appropriate)
- AE review
- Cystoscopy and urine cytology for evaluation of response (Sections 10.2.1 and 10.2.2)
- Biopsy of remaining lesions (if applicable; Sections 10.2.1 and 10.2.2)

The following visits apply only to patients with CR at Visit 7.

10.1.5 ***Monthly Telephone Contact Visits (Visits 8*, 9*, 11*, 12*, 14*, and 15*) * ± 1 week***

At Visits 8, 9, 11, 12, 14, and 15 patients will be contacted by phone to check for the following:

- Concomitant medication review
- AE review

10.1.6 ***Visits 10* and 13* (Months 6 and 9)* ± 2 weeks***

The following procedures will be performed at Visits 10 and 13 (Months 6 and 9, respectively):

- Administer QLQ-NMIBC24 questionnaire
- Concomitant medication review
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature)
- Body weight (Visit 13 only)
- Clinical laboratory tests (serum chemistry and hematology)
- Urinalysis
- AE review
- Cystoscopy and urine cytology for evaluation of recurrence (see Section 10.2.4)

10.1.7 ***End of Study Visit, Visit 16 (Month 12) ± 2 weeks***

The following procedures will be performed at Visit 16 (Month 12):

- Administer QLQ-NMIBC24 questionnaire

- Concomitant medication review
- Full physical examination
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature)
- Clinical laboratory tests (serum chemistry and hematology)
- Urinalysis
- AE review
- Cystoscopy and urine cytology for evaluation of recurrence (see Section 10.2.4)

10.1.8 Unscheduled Visits

When required, based on patient needs relating to the study, unscheduled visits can occur. The following procedures are recommended, subject to the investigator's judgement:

- Administer QLQ-NMIBC24 questionnaire if indicated (i.e., early termination)
- Concomitant medication review
- Vital signs (blood pressure, heart rate, respiration rate, and body temperature)
- Clinical laboratory tests (serum chemistry and hematology)
- Urinalysis
- AE review
- Cystoscopy/urine cytology (if indicated by reasons for patient visit)

10.2 Efficacy Assessments

10.2.1 Measurements for Evaluation of Response at 3 MONTH Visit

Assessment of response will be based on the following:

- Visual observation (cystoscopy)
- Biopsy of remaining lesions, if applicable (non-CR or suspected tissue)
- Voiding urine cytology

10.2.2 Evaluation of Response

Patient response will be evaluated according to the following criteria:

- **CR**: A patient will be considered to have had CR if there is NDD. To determine NDD, the following conditions should be fulfilled:
  1. If visual assessment indicates no remaining tumors and urine cytology is negative, the patient has NDD and CR. In the event that the bladder is free of tumor endoscopically, but the cytology is positive, the investigator is required to exclude urothelial carcinoma of the upper tract and occult carcinoma of the bladder or urethra. If UTUC is confirmed, the patient will be considered as CR.
  2. If any remaining lesions appear, even if they appear necrotic, the physician should biopsy the lesion(s). If a biopsy is taken from the necrotic lesion and found to be

negative, the patient should be classified as having CR; if positive for cancer, the patient should be classified as non-CR.

- **Non-CR:**
  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 non-CR. Note that biopsy results showing PUNLMP are not considered cancer and in such cases the patient would be considered CR.
- **Recurrence**: For patients with CR at the 3 MONTH Visit, recurrence will be assessed at Study Visit 10, Visit 13, and Visit 16.
- **If evidence of disease is identified, patients will be staged according to their local Investigator practice**. Progression is defined as change in either stage according to the Tumor-Node-Metastases (TNM) classification or grade according to the 2004 World Health Organization (WHO) classification of tumors.

  Since the patient is recruited into the trial as a patient with LG NMIBC (based on a small biopsy for LG confirmation), it is unlikely that the tumor will progress to HG during the 6-week study medication period.

10.2.3 Assessment of Tumor Progression

Diagnosis of bladder cancer at the 3 MONTH Visit with an increase in stage or grade compared to baseline will be tracked; however, it likely does not represent true progression for the following reason:

- The overall risk of progression for patients with LG papillary NMIBC at intermediate risk of recurrence ranges from 5 to 20% at 1 and 5 years (Sylvester, 2006). A 12-week interval, during which the patient is exposed to MMC treatment, is not considered long enough for progression to occur in patients with non-invasive UC.

Upstaging/upgrading detected at the 3-MONTH Visit will be recorded, and the overall incidence will be compared with that reported in the literature.

10.2.4 Assessment of Tumor Recurrence

Follow-up will be conducted in patients who were defined as having CR at the 3 MONTH Visit.

Starting with the first follow-up visit (Study Visit 10, Month 6) and continuing at Visit 13 and 16 (Months 9 and 12), information regarding disease status based on cystoscopy, cytology, and biopsy (when applicable) should be recorded. If a patient is defined as having recurrence, complete documentation should be obtained. If a patient has a positive urine cytology and/or a positive biopsy for cancer, they are considered as having urothelial cell cancer with likely recurrence. If urine cytology is positive but the biopsy is negative, the patient should be evaluated for the presence of UTUC, either by repeat CT Urogram or by retrograde pyelogram. In cases where CT Urogram or retrograde pyelogram are contraindicated, MRI may be performed. If the patient is positive for UTUC that was not present at baseline and there is no evidence of tumor within the bladder, this is considered new disease and the patient remains a CR for their NMIBC.

10.2.5 Pathological Evaluation

Biopsies and urine cytology specimens obtained at screening or any other visit should be evaluated by the local institutional pathologist.

10.3 Safety and Other Assessments

10.3.1 The safety of the study medication will be assessed by the following:

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

10.3.2 Quality of Life Assessment EORTC QLQ – NMIBC24

The QLQ- NMIBC24 is a 24-item validated, evidence-driven survey that assesses Health Related Quality of Life (HRQOL) for patients with intermediate to high risk NMIBC (Appendix 1). It is designed to be administered at baseline and at, 3, 6 and 12-month intervals. The NMIBC24 is the only instrument exclusively designed to compare HRQOL between non-muscle-invasive treatment modalities.

10.4 Adverse Events and Serious Adverse Events

10.4.1 Definition of Adverse Events

An AE means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 Code of Federal Regulations [CFR] 312.32 [a]). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory, physical examination, or vital signs finding), 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). 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. AEs must be recorded in the eCRF using CTCAE to avoid the use of vague, ambiguous, or colloquial expressions. The investigator shall evaluate all AEs in terms of severity and their relationship with the product being tested, indicating the test results and the measures to be taken.

10.4.2 Definition of Serious Adverse Events

An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include

allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

*10.4.3 **Classification of an Adverse Event***

10.4.3.1 Intensity of Event

The intensity of an AE is to be graded by the investigator according to CTCAE version 4.03. General rules are as follows:

0 **No AE** (or within normal limits)

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

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

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

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

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

10.4.3.2 Relationship to Study Medication

All AEs must have their relationship to study medication assessed by the clinician who examined and evaluated the patient based on temporal relationship and his/her clinical judgment. In a clinical trial, the study product must always be suspect. Investigators will be asked to grade each AE as either related or unrelated.

10.4.3.3 Expectedness

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

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 this protocol or the Investigator's Brochure, 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.

*10.4.4 **Time Period and Frequency for Event Assessment and Follow-Up***

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

All AEs, including local and systemic reactions not meeting the criteria for SAEs, will be captured on the appropriate eCRF. Information to be collected includes event description, time of onset, clinician's assessment of intensity, relationship to study product (assessed only by those

with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution/stabilization.

Any medical condition that is present at the time that the patient signs the informed consent form (ICF) until the first study drug administration will be considered as baseline and recorded as medical history. However, 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 drug administration until 30 days after the last dose of study medication will be considered as treatment emergent adverse events (TEAEs).

Changes in the intensity of an AE will be documented to allow an assessment of the duration of the event at each level of intensity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. The investigator or designated investigational staff member will record the start date of all reportable events. Events will be followed for outcome information until resolution or stabilization and the dates of outcome must be recorded.

10.4.5 ***Adverse Event Reporting***

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 about the above by writing using the relevant form signed by the investigator, to be sent by email/fax within 24 hours after its occurrence first came to his/her knowledge.

10.4.6 ***Serious Adverse Event Reporting***

The investigator will immediately report to the sponsor any SAE, whether or not considered study medication-related, including those listed in the protocol or Investigators Brochure and must include an assessment of whether there is a reasonable possibility that the study medication caused the event. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol, unless there is evidence suggesting a causal relationship between the study medication and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the Sponsor.

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 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 IND safety report of potential serious risks, from clinical trials 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.

10.4.6.1 SAE Reporting Instructions

The investigator must inform the sponsor within 24 hours of becoming aware of an SAE with an email to:

safety@urogen.com with copies to sponsor@urogen.com

In addition, initial SAE/Death/Pregnancy must be recorded in the electronic Case Report Form (eCRF) within 24 hours of becoming aware of the event.

10.4.7 Reporting Events to Patients

Not applicable.

10.4.8 Adverse Events of Special Interest

Adverse events of special interest are defined by the FDA (E2F Development Update Safety Report) as an AE, serious or nonserious, which is of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Events of Special Interest that may require expedited reporting and/or safety evaluation include, but are not limited to, the following:

1. Overdose of an IP
2. Suspected abuse/misuse of IP
3. Inadvertent or accidental exposure to IP
4. Medication error involving IP (with or without patient/patient exposure to the Sponsor medicinal product, e.g., name confusion)
5. Identified significant safety issue either from an individual case report or review of aggregate data

In addition,

lists specific AEs defined as AESIs with suggested actions to be taken to address them.

Table 3 Adverse Events of Special Interest

Adverse Events of Special Interest	Suggested Method to Address
Allergic reaction to MMC (CTCAE Grade 3 or 4)	Discontinue study medication and continue to follow patient off medication per the protocol (Section 9.1).
Unexpected ADR (CTCAE Grade 3 or 4)	Laboratory tests, physical examination, vital signs.
Voiding interruption due to urethral/penile edema (unrelated to prostatic hypertrophy)	Phone calls to the patients, input/output monitoring while patient is at the clinic pre- and post-instillation, physical examination.
Indication of bone marrow suppression	Hematologic laboratory tests, treatment suspension to allow for a recuperation period.
LUTS (CTCAE Grade 3 or 4)	Anti-cholinergic agents as well as local/systemic analgesics as needed.

ADR = adverse drug reaction; AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; LUTS = lower urinary tract symptoms; MMC = Mitomycin C.

10.4.9 Reporting of Pregnancy

In the event of a patient becoming pregnant, the investigator shall immediately discontinue study treatment and ensure expedited reporting of the event (see Section 10.4.5). The pregnancy will be followed to term and the outcome reported.

10.5 Other Safety Assessments

10.5.1 Laboratory Assessments

Samples for hematology and serum chemistry assessments will be taken according to the SoA in Section 1.3 and tested at the local laboratory. The amount of blood required for hematology and serum chemistry tests per visit is 15 to 20 mL. The assessments to be performed are listed in Table 4. Additional tests may be part of a clinical site's local lab's standard panel and therefore reported along with these specified tests.

10.5.1.1 Other significant laboratory derangements

If at any time the investigator identifies myelosuppression or other significant laboratory derangements during the study defined by the parameters below, treatment may be postponed for up to 4 weeks until laboratory values improve:

- Absolute neutrophil count ≥1,000/µL (≥1.0×10^9/L),
- Platelets ≥80,000/µL (≥80×10^9/L)
- AST (SGOT)/ALT (SGPT) ≥5 × upper limit of normal (ULN)
- ALP ≥2.5 institutional ULN
- For patients whose baseline GFR is ~30 mL/min/1.73m^2, decreases of up to 15% will be allowed
- For patients with normal baseline creatinine, increases of up to 2x will be allowed
- For all other patients, changes in creatinine should not result in GFR less than 30mL/min/1.73m^2

10.5.2 ***Pharmacokinetic (PK) Assessments***

At select sites, six (6) patients will be asked to participate and consent to provide blood samples for PK analysis. On the day of first instillation, this subset of patients will provide blood samples at 0 hours (pre-instillation), 0.5, 1, 2, 3, 4, 5, and 6 hours post instillation. Sites will be encouraged to use a catheter to lessen the number of needle sticks to the patient. Patients will be required to remain in the clinic for approximately 6 hours post instillation or agree to return for each blood draw at the appropriate time. The total amount of blood drawn for PK will be approximately 40 mL.

Table 4 Laboratory Safety and Pharmacokinetic (PK) Assessments

Liver Function Tests:	**Kidney Function Tests:**	**Hematology Tests:**	**PK**
SGOT/AST	Creatinine	CBC, including red blood cell indices and white blood cell differential	**MMC Levels** (6 Patients)*
SGPT/ALT	Blood urea nitrogen	Platelet count	Plasma
GGT	Uric acid		
Alkaline phosphatase	Sodium		
Total bilirubin	Potassium		
Direct bilirubin	Phosphorus		
Albumin	Calcium		
Total protein	Bicarbonate		
	Chloride		
	eGFR (calculated in EDC)		

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; GGT = gamma-glutamyltransferase; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.
* The amount of blood required for each MMC PK level measurement time point is 5 cc; approximate total of 24 cc for PK visit. PK samples will be kept in -70 freezer in a light-blocking box until shipped to central lab for analysis.

10.5.3 ***Urinalysis***

At the visits specified in Section 1.3, samples will be taken for urinalysis, including culture and sensitivity at the screening visit.

10.5.4 ***Physical Examination Findings***

At the visits specified in Section 1.3, a full physical examination or urology-oriented physical examination will be performed. The patient's physical condition will be examined and documented. This includes examination of main body systems, with focus on the urinary system. The examinations to be performed are summarized in Table 5.

Table 5 Physical Examinations

General/Full Physical Examination will be performed at Screening Visit and Study Visit 16	Urology–Oriented Physical Examination will be performed at Screening Visit and Study Visits 1, 4, and 7, and for CR patients at Visits 8, 9, 11, 12, 14, 15, and 16
General appearance Cardiovascular system Respiratory system HEENT (head, eyes, ears, nose, and throat) and neck Abdomen Extremities Neurologic system Skin	Urethral meatus Perineal skin and mucus membranes Scrotum and testes (for male patients) Lymphadenopathy Rectal examination (Screening visit only) Bimanual examination (female patients – Screening visit only)

At each visit, the following vital signs measurements are to be taken after having the patient rest quietly in the sitting position for at least 3 minutes: blood pressure, heart rate, respiration rate, and body temperature.

10.5.5 Pregnancy Test

A urine pregnancy test will be conducted in female patients of childbearing potential at the Screening Visit and at Study Visits 7. If positive, a serum pregnancy test will be performed to verify. A female is considered of childbearing potential unless:

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

10.5.6 Reporting Unanticipated Problems to Patients

Not applicable.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical Hypotheses

Analyses are descriptive and exploratory in nature and no formal hypotheses will be tested.

11.2 Sample Size Determination

Approximately 66 patients will enter the study, with 60 expected to complete, assuming 10% dropout rate. Given the patient population under study, i.e., those at intermediate risk of recurrence, a more conservative CR rate than previous studies of UGN-102 in the treatment of LG NMIBC has been assumed. The primary objective will be successfully achieved if complete responses from 36 out of 60 patients with CR rate of 60% will be observe, which would yield a 95% confidence interval of (46.5%, 72.4%) based on the exact (Clopper-Pearson) binomial distribution.

11.3 Populations for Analyses

11.3.1 ***Intent-to-Treat (ITT) Analysis Set (Safety Analysis Set)***

The Intent-to-Treat (ITT) Analysis set will consist of all patients who have been enrolled into the trial and who have received any instillation of UGN-102 preparation. This analysis set, which will include all data captured in the database for these patients, will serve as the primary set for the primary efficacy endpoint analysis and will serve as the analysis set for the secondary safety endpoint analyses.

11.3.2 ***Modified Intent-to-Treat (mITT) Analysis Set***

The Modified Intent-to-Treat (mITT) Analysis Set will consist of all patients who have been enrolled into the trial, who have a confirmed diagnosis of LG NMIBC based on the local pathology reading, who received at least 1 instillation of UGN-102 preparation, and who have undergone the 3 MONTH Visit (since it is the first visit for the outcome evaluation).

11.3.3 ***Per Protocol (PP) Analysis Set***

The Per Protocol (PP) Analysis Set will consist of all patients who have been enrolled into the trial, who have a confirmed diagnosis of LG NMIBC based on the local pathology reading, who received all 6 weekly instillations of UGN-102 preparation, and who have undergone the 3 MONTH Visit. Patients who are identified as HG by local pathology reading at the 3 MONTH visit will be excluded from this analysis set. This analysis set, which will include all data captured in the database for these patients, will serve as supportive data for the primary efficacy endpoint analysis.

11.3.4 ***Complete Response at Primary Outcome Analysis Set***

The Complete Response at 3 MONTH Visit (3 $MONTH_{CR}$) Analysis Set will consist of all patients who achieved CR at the 3 MONTH Visit (Study Visit 7). This analysis set, which will include all data captured in the database for these patients, will serve as the primary set for the secondary efficacy endpoint analysis.

11.4 Statistical Analyses

A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to database lock. The SAP will supersede this statistical analysis section.

11.4.1 ***General Approach***

All measured variables and derived parameters will be listed individually and, if appropriate, tabulated using descriptive statistics. For categorical variables, summary tables will be provided giving sample size, absolute and relative frequency, and 95% confidence interval (CI) for proportions using the exact approach. For continuous variables, summary tables will be provided giving sample size, arithmetic mean, standard deviation (SD), coefficient of variation (if appropriate), median, minimum and maximum, percentiles, and 95% CI for means of variables. For variables with non-normal distribution, medians and interquartile range (IQR) will be calculated, and the appropriate non-parametric tests will be applied.

11.4.2 ***Analysis of the Primary Efficacy Endpoint***

The analysis of the primary endpoint will test the CR rate defined as percentage of patients with CR at the 3 MONTH Visit using the ITT Analysis Set.

A test for binomial proportions (SAS® PROC FREQ with binomial option) will be used to derive the exact 95% CI for the true CR rate.

11.4.3 ***Sensitivity Analysis of the Primary Efficacy Endpoint***

Sensitivity analysis of the primary endpoint will include repeat of the primary efficacy analysis (Section 11.4.2) using the PP Analysis Set, i.e., including only patients who received all 6 instillations of UGN-102 preparation and are LG at baseline (patients with HG at 3 MONTH Visit will be excluded).

11.4.4 ***Analysis of the Secondary Efficacy Endpoints***

One key secondary endpoint is pre-defined for this trial: the durable complete response (DCR) rate at 6, 9, and 12 months after the first instillation of UGN-102 preparation, defined as the percentage of patients who continue to display CR at Study Visits 10, 13, and 16, respectively.

Analysis will use the 3 $MONTH_{CR}$ Analysis Set, implying that the denominator for this analysis will be the number of patients who demonstrated CR at the 3 MONTH Visit. Patients who withdraw early from the trial between the 3-MONTH Visit and Study Visit 16 for whom follow-up data regarding the disease status (i.e., recurrence) is not available will be treated as follows:

- Patients who discontinue during this time window due to adverse reactions from the study medication, lack of efficacy, death, or any other cancer-related reason will be considered as treatment failures for the purpose of this analysis.
- Patients who withdraw during this time window due to reasons other than those given above will be excluded from the analysis.

A test for binomial proportions (SAS® PROC FREQ with binomial option) will be used to derive the exact 95% CI for the true DCR rate at 6, 9, and 12 months.

11.4.5 ***Safety Analyses***

11.4.5.1 Adverse Events and Serious Adverse Events

Adverse events will be recorded from the time a patient has signed the informed consent until 30 days after the last instillation of study medication. AEs reported by the investigators will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

The following will be incorporated into the analysis of AEs:

- All analyses to be provided will include coded AEs.
- AE analyses will include both all AEs and treatment-emergent AEs (TEAEs), i.e., events that started on the day of first administration of study medication or afterwards, or that were present before first administration of study medication and increased in intensity

after first administration of study medication. Listings of both TEAEs and non-TEAEs will be provided.

- The incidence (number of patients) and frequency (number of events) of TEAEs will be provided, broken down by System Organ Class (SOC) and by Preferred Term (PT) according to MedDRA.
- The incidence (number of patients) and frequency (number of events) of TEAEs will be provided, broken down by descending frequency by PT according to MedDRA.
- Breakdowns of TEAEs by all AE attributes will also be provided.
- Breakdowns of TEAEs by age and sex will also be provided.
- The derived dictionary used in the analyses displaying the MedDRA SOC and PT and the AE verbatim term as specified by the investigator, will be provided.
- The incidence and frequency of treatment-emergent SAEs will be provided, broken down by SOC and by PT according to MedDRA, as well as by SAE attributes and by age and sex. Listings of both treatment-emergent and non-treatment-emergent SAEs will be provided.

11.4.5.2 Laboratory Assessments

Analyses of safety laboratory data will be performed for all collected laboratory parameters. Quantitative laboratory measurements will be categorized with reference to the normal ranges as Low, Normal, or High. Shift analysis of the categorical change from baseline to each scheduled visit and to the last observed assessment will also be performed.

A list of parameters and related cut-off values defining the PCS abnormal values will be outlined by the Sponsor prior to initiation of the first trial instillation. Measurements used in the analysis are those taken following first trial instillation. The incidence tables of PCS laboratory values as well as the individual patient listing will be provided using the denominator that is the number of patients with at least 1 post-baseline administration of trial medication. Individual patients' listings of PCS measurements will also be presented.

11.4.5.3 Physical Examination

Any clinically relevant changes occurring from Screening until the last trial visit will be recorded on the Adverse Event Sections of the eCRF and reported with AEs as described above.

11.4.5.4 Vital Signs

Analyses of vital signs (blood pressure, heart rate, respiration rate, and body temperature) will be performed using descriptive statistics of vital signs before Screening, instillation, and during the trial, and by presenting changes from baseline by scheduled visit.

11.4.5.5 Concomitant Medications

The WHO drug dictionary will be used to classify medications verbatim for concomitant and pre-trial medications. Analysis of concomitant drug use will be performed in the following manner:

- Pre-instillation concomitant medications use: Analyses will include coded medications that were initiated prior to first instillation, regardless if stopped after the first instillation. An incidence table including patient counts (number of patients) and percentages broken down by Medication Class and PT will be provided.
- Concomitant medications use (post-first instillation): Analyses will include only coded medications that were administered following the first instillation, regardless if drug initiation date was before or after first instillation. An incidence table including patient counts (number of patients) and percentages broken down by Medication Class and PT will be generated.

11.4.5.6 MMC Levels (Pharmacokinetics) Profiling

Pharmacokinetic (PK) profile during the 6 hours following the first administration of UGN-102 will be based on PK sampling at 0 (pre-instillation), 0.5, 1, 2, 3, 4, 5, and 6 hours post instillation. PK will be performed with just 6 patients who provide informed consent for PK testing. Concentration data as well as PK parameters (e.g., AUC) will be provided using descriptive statistics. Plasma samples for evaluation of PK properties of MMC following instillation with UGN-102 Admixture will be collected and archived. These samples are to be used to characterize the plasma concentration of MMC during the 6 hours post instillation, which is the estimated duration of the dwell-time of UGN-102 Admixture. The PK parameters obtained, specifically the C_{max}, will be compared to the threshold of MMC plasma concentration (400 ng/mL) known to be associated with myelosuppression, as well as to the known PK profile of MMC obtained with different routes/methods of administration (e.g., intravesical instillation with WFI).

Additionally, these data, combined with data emerging from other trials may be used in population pharmacokinetic model development and analysis.

11.4.6 ***Baseline Descriptive Statistics***

Disposition data from patients who were screened but not treated, patients in the ITT, mITT, PP, and 3 $MONTH_{CR}$ Analysis Sets, as well as trial withdrawal data will be summarized using descriptive statistics.

Demographics and baseline data, as well as disease prognostic factors, medical history, and prior medications, will be summarized for the ITT Analysis Set using descriptive statistics. For continuous variables, descriptive statistics (number, mean, SD, standard error, median, minimum, and maximum) will be provided. For categorical variables, patient counts and percentages will be provided. Categories for missing data will be presented if necessary. Missing categories will be presented if necessary.

11.4.7 ***Planned Interim Analyses***

When approximately 12 patients have reached their Month 3 visit an interim analysis will be performed for primary endpoint.

11.4.8 ***Sub-Group Analyses***

To be addressed in the SAP

11.4.9 Tabulation of Individual Patient Data

Individual patient data will be listed by measure and time point.

11.4.10 Exploratory Analyses

PK and QoL will be evaluated.

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory, Ethical, and Study Oversight Considerations

12.1.1 Informed Consent Process

12.1.1.1 Consent/Assent and Other Informational Documents Provided to Patients

Consent forms describing in detail the study medication, study procedures, and risks are given to the patient, and written documentation of informed consent is required prior to initiating any study procedures and starting medication/administering study medication. The informed consent form (ICF) template is submitted with this protocol.

12.1.1.2 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/designee will explain the research study to the patient and answer any questions that may arise. 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. The patient will sign the informed consent document prior to any procedures being done specifically for the study. Patients must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the patients for their records. 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.

12.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study patients, investigator, Sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the investigator will promptly inform study patients, the IRB, and the Sponsor and will provide the reason(s) for the termination or suspension. Study patients will be contacted, as applicable, and be informed of changes to the study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to, the following:

- Determination of unexpected, significant, or unacceptable risk to patients
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

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

12.1.3 ***Confidentiality and Privacy***

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 monitor, other authorized representatives of the Sponsor, representatives of the IRB, regulatory agencies, or pharmaceutical company supplying the study product may inspect all documents and records required to be maintained by the investigator, including, but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

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.

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.

12.1.4 ***Future Use of Stored Specimens and 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.

12.1.5 ***Safety Oversight***

Safety oversight will be under the direction of the Sponsor. Safety oversight will be independent from the study conduct and free from conflict of interest.

12.1.6 ***Clinical Monitoring***

The sponsor will perform on-site monitoring visits as frequently as necessary, depending on recruitment frequency at each site. The monitor will record dates of the visits in a trial 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 trial-related documents. The monitor will meet with the investigator on a regular basis during the trial to provide feedback on the trial conduct. Further details of clinical site monitoring will be provided in a Study Monitoring Plan (SMP). The SMP will describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

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

12.1.7 ***Quality Assurance and Quality Control***

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database. Any missing data or data anomalies will be communicated to the sites for clarification/resolution.

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

The investigational site will provide direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor and inspection by local and regulatory authorities.

*12.1.8 **Data Handling and Record Keeping***

12.1.8.1 Data Collection and Management Responsibilities

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

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. It is the sponsor's expectation that data required by the protocol will be entered by the clinical site staff no later than 5 days from each visit.

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.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered in the eCRF using a 21 CFR Part 11-compliant electronic data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

12.1.8.2 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 medication. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed 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.

*12.1.9 **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.

All important deviations related to study inclusion or exclusion criteria, conduct of the trial, 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 according to their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

Protocol waivers are not allowed. If a patient's eligibility is in question, please contact the sponsor.

12.1.10 Publication and Data Sharing Policy

Not applicable.

12.1.11 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 trial 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 trial. 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.

12.2 Additional Considerations

12.2.1 Finance and Insurance

12.2.1.1 Finance:

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

12.2.1.2 Insurance:

The trial will be covered in accordance with local requirements. Insurance coverage will be provided by the Sponsor. In case of any damage or inquiry occurring to a patient in association with the IP or the participation in this trial, the Sponsor will contact the insurance company that covers the liability of the Sponsor, the investigator, and other persons involved in the trial, in compliance with the laws in the country where the trial takes place.

13 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Changes	Brief Rationale
4.0		• Removal of maintenance monthly instillations visits, replaced by telephone contacts for safety follow-up at months 8, 9, 10, 11, 12, 13, 14, and 15 in sections 1.1, 1.2, 1.3.2, 6.1, 8.1.3, 10.1.5, and 10.1.6.	Sponsor decision
		• Additional study design rationale added to section 6.2: "Based on data from an ongoing Phase 3 trial in a similar indication, UTUC, monthly maintenance treatments do not appear to have a meaningful effect on durability of response in those patients who were CR at the 3-month assessment (primary endpoint)."	Revised study design rationale
		• Reference to monthly study drug instillations removed in sect. 8.1.3	Sponsor decision
		• Addition of the word "bladder" in sect. 8.5	Due to oversight, the word "bladder" had been omitted.
		• Removal of pregnancy test at months 6, 9, and 12 in sect. 10.1.6, 10.1.7, and 10.5.5	Patients will have been off study drug for at least 4 months
		• Additional reference added to section 13	To support change study design

Version	Date	Description of Changes	Brief Rationale
3.0	20Jan2019	• QoL questionnaire added as a Tertiary/Exploratory endpoints in Summary sect. 5 and sect. 11.4.10	Sponsor decision

Version	Date	Description of Changes	Brief Rationale
		• Adjustments to the SoA in section 1.3.1	
		• Several new abbreviations added to the abbreviations section	Clarification
		• Updates to contact information in sect. 3	To be consistent with protocol additions
		• Screening period revised based on timing of eligibility biopsy, sect. 6.1 and 10.1.1	New information
		• Additional instructions in case of symptomatic and asymptomatic UTI at treatment visits, sect. 8.5	To be consistent with prior administrative letter
		• Additional instructions on permissible study personnel for instillation of study drug 10.1.2	Clarification
		• Addition of QLQ-NMIBC24 questionnaire at applicable study visits in sect. 10.1 and 10.3.2	Clarification
		• Update to sample size section 11.2	New study procedure
		• Addition of an interim analysis	
		• Minor typographical corrections and clarifications throughout the document	Clarification
		• Additional reference added to sect.	Sponsor decision
		• Addition of sect.15 Appendix 1 QLQ-NMIBC24 sample	NA
			Reference for QLQ-NMIBC24 validation

Version	Date	Description of Changes	Brief Rationale
2.0	10AUG2018	• Study Title: removal of "a chemoablation agent" replaced with "as primary chemoablative therapy"	To clarify that this treatment is being studied as first line therapy in lieu of TURBT
		• Abbreviations moved to Section 2	For ease of reference
		• Section 3 Key Roles and Study Contact Information added	Additional section
		• Sect. 7.1: ○ Reduction of the 12-week screening biopsy period requirement to 6 weeks so as to shorten the period between diagnosis and the 3-month primary endpoint evaluation	FDA request
		○ New definition of recurrence in inclusion criterion 4c	FDA request
		○ Addition of inclusion criterion 7 requiring baseline minimum organ and bone marrow function blood levels	FDA request
		• Sect. 10.5.2: Addition of PK analysis in a subset of patients and the required collection timepoints at the enrollment visit.	FDA recommendation
		• Sect. 11.4.5.6: Description of the PK profiling	FDA recommendation
		• Minor typographical corrections and clarifications throughout the document	NA

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UroGen Study TC-UT-03, A Phase 3 Multicenter Trial Evaluating the Efficacy and Safety of MitoGel™ (UGN-101) on Ablation of Upper Urinary Tract Urothelial Carcinoma

15 APPENDIX 1

15.1 EORTC QLQ – NMIBC24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:

		Not at all	A little	Quite a bit	Very much
31.	Have you had to urinate frequently during the day?	1	2	3	4
32.	Have you had to urinate frequently at night?	1	2	3	4
33.	When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34.	Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35.	Have you had difficulty going out of the house, because you needed to be close to a toilet?	1	2	3	4
36.	Have you had any unintentional release (leakage) of urine?	1	2	3	4
37.	Have you had pain or a burning feeling when urinating?	1	2	3	4
38.	Did you have a fever?	1	2	3	4
39.	Did you feel ill or unwell?	1	2	3	4
40.	Did you have trouble arranging your life around the repeated bladder treatment appointments (cystoscopies or instillations)?	1	2	3	4
41.	Did you worry about having repeated bladder treatments (cystoscopies or instillations)?	1	2	3	4
42.	Were you worried about your health in the future?	1	2	3	4
43.	Did you worry about the results of examinations and tests?	1	2	3	4
44.	Did you worry about possible future treatments?	1	2	3	4
45.	Did you have a bloated feeling in your abdomen?	1	2	3	4
46.	Have you had flatulence or gas?	1	2	3	4

During the past 4 weeks:

		Not at all	A little	Quite a bit	Very much
47.	To what extent were you interested in sex?	1	2	3	4
48.	To what extent were you sexually active (with or without sexual intercourse)?	1	2	3	4
49.	**For men only:** Did you have difficulty gaining or maintaining an erection?	1	2	3	4
50.	**For men only:** Did you have ejaculation problems (e.g. dry ejaculation)?	1	2	3	4

Please answer the following 4 questions only if you have been sexually active during the past 4 weeks:

		Not at all	A little	Quite a bit	Very much
51.	Have you felt uncomfortable about being sexually intimate?	1	2	3	4
52.	Have you worried that you may contaminate your partner during sexual contact with the bladder treatment you have been receiving?	1	2	3	4
53.	To what extent was sex enjoyable for you?	1	2	3	4
54.	**For Women only:** did you have a dry vagina or other problems during intercourse?	1	2	3	4

ENGLISH

Description of Change: 10.5.5 should read: A urine pregnancy test will be conducted in female patients of childbearing potential at the screening Visit and at Study Visit 7. And the summary of changes should say: Removal of pregnancy test at months 6, 9, and 12 in sect. 10.1.6, 10.1.7, and 10.5.5

Action Name	User Name	Title	Date
Created By	Shira Simis	QA Team Leader	13-Apr-2019
Review	Robert Kirshoff	S. Director Clinical Development	14-Apr-2019
Approve	Gilad Bernadsky	VP QA	15-Apr-2019
Approve	Elyse Seltzer	SVP Clinical Development, Medical Affairs & PV	15-Apr-2019
Approve	Jim Ottinger	SVP Regulatory Affairs	15-Apr-2019