Trial Title:

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

Protocol ID: TC-UT-03-P

Country: USA

1. Statement of Compliance

The trial will be conducted in accordance with the International Conference on Harmonization guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Patients (21 CFR Part 50), and the Clinical Terms of Award. All personnel involved in the conduct of this trial have completed human patients' protection training.

2. Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is privileged or confidential and may not be further disclosed by them. These restrictions on disclosure will apply equally to all future information supplied to you that is indicated as privileged or confidential

3. Investigator's Statement and Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations, local regulations and ICH guidelines.

Principal Site Investigator:

Principal Site Investigator:

Name/Title	Site name	Signature	Date

Table of Contents

1.	Statement of Compliance	1
2.	Confidentiality Statement	1
3.	Investigator's Statement and Signature Page	2
4.	Abbreviation List	6
5.	Protocol Synopsis	8
6.	Key Roles and Contact Information	17
7.	Introduction and Background	18
7.1.	Upper tract urothelial carcinoma (UTUC)	18
7.2.	Current treatment:	18
7.3.	Investigational Product: MitoGel™ (TC-3 and MMC)	21
7.4.	Justification of Trial Design	24
7.5.	Potential Risks and Benefits	26
8.	Trial Objectives	27
8.1.	Safety	27
8.2.	Primary Efficacy	28
8.3.	Key Secondary Efficacy	28
8.4.	Secondary Efficacy	28
9.	Trial Endpoints	28
9.1.	Safety Endpoints	28
9.2.	Efficacy Endpoints	28
9.3.	Trial Design	30
9.4.	Evaluation plan at PDE	32
9.5.	Evaluation plan at follow-up	33
9.6.	Central Lab Pathologist	34
10.	Trial Population and Eligibility Criteria	34
10.1.	Inclusion Criteria	34
10.2.	Exclusion Criteria	36
11.	Investigational product (IP) - MitoGel™ Kit	38
11.1.	MitoGel™ Kit Packaging and Labeling	38
11.2.	Investigational Product Acquisition, Dispatch, and Storage	41
11.3.	MitoGel™ Admixture Dosage, Preparation, Dispensing and Administration	43
11.4.	IP Accountability	46
11.5.	Replacement of Unusable MitoGel™ Kits	47
11.6.	Assessment of IP compliance	47
11.7.	Destruction of IP	47
12.	Safety Evaluation	48
12.1.	Safety Assessment Prior and During the Treatment Period:	48
12.2.	Telephone Contact 24–32 Hours Post-treatment	49
12.3.	VAS Questionnaire - Pain Assessment During Treatment	49
12.4.	Tests for Assessment of Safety	49
13.	Trial Conduct and Procedures	50
13.1.	Patient Eligibility Review and Enrolment to the Trial	50
13.2.	Screening Visit (V0): -4 to -1 weeks	51
13.3.	Treatment Visits	54
13.4.	LAB 1 (V7) & LAB 2 (V8):	63
13.5.	Primary Disease Evaluation Visit (PDE, V9)	64
13.6.	CR Patients Maintenance Instillations (Maintenance Visits)	65
13.7.	Follow-up Visits (V12, V15, V18, V21)	65
13.8.	Unscheduled Visit	66
13.9.	Treatment Discontinuation	66

14.	**Schedule of Events**	**68**
14.1.	**Part I - All Patients - Up to PDE Visit**	**68**
15.	**Evaluation of Response**	**75**
15.1.	**Tumor Measurements and Classification of Partial Response (PR)**	**75**
15.2.	**Assessment of UC Tumor Progression**	**76**
15.3.	**Assessment of UC Tumor Recurrence**	**76**
15.4.	**Pathological Evaluation:**	**77**
16.	**Trial Flow-Chart Per Patient**	**78**
17.	**Patients Withdrawal From Treatment or/and Follow Up, and Trial Completion**	**79**
17.1.	**Criteria for Patient withdrawal from MitoGel Treatment:**	**79**
17.2.	**Definition of Trial Completion**	**81**
17.3.	**Replacement of Individual Patients**	**81**
18.	**Statistical Methodology**	**81**
18.1.	**Significance Level**	**82**
18.2.	**Sample Size Rationale**	**82**
18.3.	**Futility Analysis**	**83**
18.4.	**Analysis Sets**	**83**
18.5.	**Patient Disposition**	**85**
18.6.	**Demographic and Baseline Characteristics**	**85**
18.7.	**Efficacy Analyses**	**85**
18.8.	**Evaluation of Safety**	**88**
19.	**Management of Adverse Events**	**91**
19.1.	**Definitions**	**91**
19.2.	**Reporting procedures**	**93**
19.3.	**Data Monitoring Committee (DMC)**	**97**
20.	**Concomitant Medications**	**98**
21.	**Ethical Considerations and Confidentiality**	**98**
21.1.	**Informed Consent**	**98**
21.2.	**Ethics Committee and Competent Authorities**	**99**
22.	**Quality Control and Quality Assurance:**	**100**
22.1.	**Source Documentation**	**100**
22.2.	**Record Retention**	**101**
22.3.	**Clinical Monitoring**	**101**
22.4.	**Protocol Deviations**	**102**
22.5.	**Audit and Inspection**	**102**
23.	**Trial Systems**	**103**
23.1.	**Data Collection and Management Responsibilities**	**103**
23.2.	**Procedures & Timelines for Data Capturing**	**103**
23.3.	**Acknowledgment of MitoGel™ Kit Shipment Receipt**	**105**
23.4.	**AG MedNet System for Images Upload**	**105**
24.	**Trial Completion/Termination**	**105**
24.1.	**Trial Completion**	**105**
24.2.	**Trial Termination**	**105**
25.	**Changes in the Conduct of the Trial:**	**106**
25.1.	**Protocol Amendments**	**106**
26.	**Study Leadership**	**106**
27.	**Administrative and Regulatory Details**	**107**
27.1.	**Registration of Clinical Studies and Disclosure of Results**	**107**
27.2.	**Ownership of Data**	**107**
27.3.	**Conflict of Interest Policy**	**107**
27.4.	**Final Report and Publication of the Results**	**107**

27.5. Finance and Insurance 108
28. Bibliography: 109
Appendix I: Clinical Evaluation 116
Appendix II: Vital Signs 117
Appendix III: Required Lab Tests 118
Appendix IV: Questions 24–32 hours Post Treatment Visit 119
Appendix V: Karnofsky & ECOG Scores (Oken et al, 1982) 120
Appendix VI: Recommended Antimicrobial Prophylaxis for Urologic Procedure 121
Appendix VII: Collection and Handling of Plasma Samples for MMC Pharmacokinetics 122
Appendix VIII: CTACAE 4.03 Severity Grades, and Allergic Reaction Grades 123
Appendix IX: Protocol Amendment Version 6.0 – Summary of Changes 124

4. Abbreviation List

ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BCG	Bacille de Calmette et Guérin
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CI	Confidence Interval
CIS	Carcinoma In Situ
CR	Complete response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EC	Ethical Committee
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capturing system
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
FU	Follow Up
FPI	First Patient In
g	Gram
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HG	High Grade
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IFP	Instructions for Pharmacy
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Board
LG	Low Grade
LPO	Last Patient Out
mg	Milligram
mL	Milliliter

mITT	Modified Intent-to-Treat
MitoGel™	MitoGel™ Admixture, of TC-3 Hydrogel Mixed with Mitomycin C, using the Kit's components
MMC	Mitomycin C
NCI	National Cancer Institute
NDD	No detectable Disease
NMIBC	Non Muscle Invasive Bladder Cancer
NR	No Response
NSP	Nephron-Sparing Procedures
ORR	Objective Response Rate
PCS	Potentially Clinically Significant
PDE	Primary Disease Evaluation
PG	Performance goal
PK	Pharmacokinetics
PQC	product quality complaint
PR	Partial Response
PP	Per Protocol
RNU	Radical nephro-ureterectomy
SAE	Serious Adverse Event
SE	Safety Evaluation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	Standard of Care
SUSAR	Suspected Unexpected Serious Adverse Events Response
TC-3	TC-3 Sterile Hydrogel by UroGen Pharma Ltd.
TEAE	Treatment Emergent Adverse Events
TNM	Tumor Node Metastases
TURBT	Transurethral Resection of Bladder Tumor
UADR	Unexpected Adverse Drug Reaction
UC	Urothelial carcinoma
ULN	Upper limit of normal
URS	Ureteroscopy
UPJ	Ureteropelvic Junction
UUT	Upper Urinary Tract
UTI	Urinary tract infection
UTUC	Upper Tract Urothelial Carcinoma
WFI	Water for Injection

5. Protocol Synopsis

Trial Title	**A Phase 3 Multicenter Trial Evaluating the Efficacy and Safety of MitoGel™ (UGN-101) on Ablation of Upper Urinary Tract Urothelial Carcinoma**
Protocol Number	**TC-UT-03**
Clinical Phase	Phase III and Phase IIIb
Investigational Product	MitoGel™ Kit
Route of Delivery	Instillation to the Upper Urinary Tract (UUT)
Indication	Treatment for Upper Tract Urothelial Carcinoma (UTUC)
Sponsor	UroGen Pharma Ltd. 9 Ha'Ta'asiya St., Ra'anana, Israel
Trial Centers	Approximately 45 medical centers across the United States, Canada, Europe and Israel.
Trial Objectives:	**Safety:** • To evaluate the safety and tolerability of the MitoGel™ Admixture in UTUC patients. • To assess the pharmacokinetics profile of Mitomycin C (MMC) in plasma of a sub-group of patients treated with MitoGel™ Admixture. **Primary Efficacy Objectives:** To evaluate the tumor ablative effect of MitoGel™ Admixture in the UUT of patients with UTUC at PDE visit. **Key Secondary Efficacy Objectives:** To evaluate response durability at 12 months for patients showing CR at PDE.
	Secondary Efficacy Objectives: • To evaluate the durability of tumor ablative effect of MitoGel™ Admixture in patients who demonstrated complete response (CR) at the Primary Disease Evaluation (PDE) Visit, 3, 6 and 9 months following the PDE visit. • To evaluate the overall clinical benefit to the treatment with MitoGel™ admixture

Safety Endpoints	**Study's safety endpoints include:** • Frequency (number of events) and incidence (number of patients) of adverse events. • Changes from baseline in laboratory values and incidence of measurements defined as Potentially Clinically Significant (PCS). • Changes from baseline in vital signs assessments values and incidence of measurements of Potential Clinical Significance (PCS). • Clinically relevant Physical examinations findings. • Changes in concomitant medications (type or dose) from baseline. In addition, pharmacokinetic (PK) profile of the first MMC instillation in the blood will be examined for the first six patients. In addition, pharmacokinetic (PK) profile of the first MMC instillation in the blood will be examined for the first six patients.
Efficacy Endpoints	**Primary Efficacy Endpoint:** Complete Response (CR) defined dichotomously as "Success" if CR was confirmed at the end of the treatment period (PDE Visit), and "Failure" otherwise. **Key Secondary Efficacy Endpoint:** Long term durability of CR: This endpoint is defined only for those patients demonstrating CR at PDE visit. The endpoint is defined dichotomously as "Success" if CR was obtained at follow-up Visit 4 (12 months post PDE visit), and "Failure" otherwise. **Secondary Efficacy Endpoint** • Durability of CR defined dichotomously as "Success" if CR was achieved at PDE visit and remained at follow-up Visit 1, Visit 2 and Visit 3 (3, 6 and 9 months post PDE), and "Failure" otherwise. This endpoint is defined only for those patients demonstrating CR at PDE visit. • Partial response at PDE visit will be defined dichotomously, similarly to the primary efficacy endpoint. For subjects with partial response at PDE visit, originally planned and actual treatments will be compared.
Trial Design	
Trial TC-UT-03 is a prospective, open label, single-arm trial, designed to assess the efficacy, safety, and tolerability of treatment with MitoGel™ instilled in the upper urinary tract of patients with non-invasive low-grade (LG), UTUC. Upon signing of informed consent, the patients will undergo a screening visit for eligibility evaluation. Eligible patients will be treated with MitoGel™ once weekly for a total of 6 times; in a retrograde fashion. Patients who demonstrate CR (based on the central lab evaluation and URS) will be treated with MitoGel™ once monthly as a maintenance therapy for a total of 11	

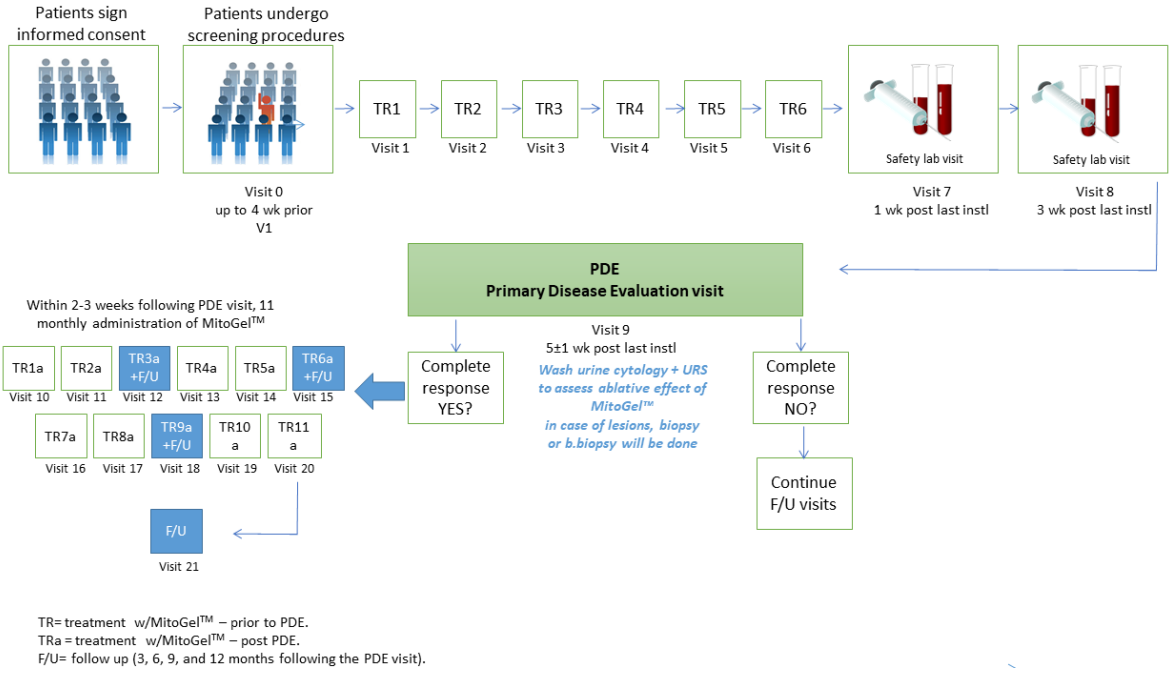
instillations or up to the first recurrence, whichever comes first.

Instillation through a nephrostomy tube may be an option if necessary upon advising with the principle coordinating investigator.

Determination of the eligibility of all patients and admission into the trial will be decided upon a case-by-case basis in consultation with the trial principal coordinating investigator Dr. Seth Lerner (slerner@bcm.edu). The sponsor will send a final approval for patient enrollment to the site.

General description of trial visits

Visit	**Timeline**
Screening (V0)	Up to 4 weeks prior to treatment
Instillations 1-6 (V1-V6)	Once weekly for 6 weeks
Safety Labs (V7-V8)	One week and 3 weeks post last instillation
Primary disease evaluation (PDE) (V9)	5±1 weeks following the last instillation visit
Maintenance Instillations (V10-V20)	Within 2-3 weeks following PDE visit, 11 monthly administration of MitoGel™
Follow up visits (FU 1-4) (V12, V15, V18, V21)	3, 6, 9, and 12 months following the PDE visit.



Investigational product: The MMC concentration of MitoGel™ to be used in this trial will be 4 mg MMC per 1 mL of TC-3 gel. The volume of the MitoGel™ to be instilled into the patient pyelocalyceal system will be individualized and will be based on volumetric measurements of the pyelocalyceal system using pyelography (average of 3 measurements) and will not exceed 15 mL (a maximum dose of 60 mg). The pyelography procedure can be

done at any time before the first treatment. The volume of MitoGel™ instilled will be 100% of the measured pyelocalyceal volume or 15 mL (whichever is lower).

Instillations process: Prior to every instillation the patient will be prescribed with sodium bicarbonate and will be instructed to consume 1.3 g of sodium bicarbonate the night prior to treatment, the morning of, and 30 min. prior to the treatment the patient will be also prescribed with a prophylaxis antibiotic to be taken to cover each treatment according to the AUA antimicrobial prophylaxis recommendations.

Prophylactic anti-allergic treatment will be given per PI discretion. Recommended regimen– Anti-histaminic agents to be taken the day before instillation, on the day of instillation and 1-3 days after the instillation. Changes in such regimen may occur per the site principal investigator medical judgment.

Diazepam (5-10 mg) (or any other relaxation pill) will be given before instillations according to the PI discretion to reduce the anxiety.

PK evaluation will take place in a subset of patient (N=6) who provided an informed consent. Blood samples will be collected at 0 (pre-dose) and 30 min, 1, 2, 3, 4, 5, and 6 hours post first MitoGel™ instillation.

Patients' safety will be monitored through the entire study by recording Adverse Events (AEs) throughout the study by:

- Frequency (number of events) and incidence (number of patients) of adverse events
- Changes from baseline in laboratory values and incidence of measurements defined as Potentially Clinically Significant (PCS).
- Changes from baseline in vital signs assessments values and incidence of measurements of Potential Clinical Significance (PCS).
- Clinically relevant Physical examinations findings

Five (5) weeks (± 1 w) following the last treatment, the PDE Visit, during which safety and efficacy will be assessed, will take place. During this visit, UT wash urine cytology will be carried out followed by URS which enables to assess visually the ablative effect of the MitoGel™. In case of remaining lesions, biopsy or brush biopsy shall be taken if applicable.

Patient demonstrating CR at PDE will undergo monthly maintenance instillations of MitoGel™ up to 11 months post PDE. Safety follow-up for these patients will be done until one month post last instillation or at the end of the follow-up period in FU visit 12, which is the earlier.

For patients who did not demonstrate Complete Response, to the extent that it is possible, all remaining tumors lesions will be biopsied. Based upon PI discretion the patients shall undergo any additional surgical or other treatment which might be deemed necessary to the patient health. The tumor lesion location, size and grade, as well as the surgical procedure or treatment provided to treat the remaining disease will be documented.

Efficacy will be assessed by the rate of CR at PDE, i.e., 5 weeks (±1 week) after last MitoGel™ treatment. The durability of response will be assessed primarily by the rate of CR

at 3 months after PDE and then every 3 months up to a one year post PDE visit.

During the FU period, disease recurrence and or progression, the type of intervention, and histopathological (where applicable) will be recorded.

DMC-An independent Data Monitoring Committee (DMC) has been assigned to this trial. Accumulating safety, tolerability and efficacy data will be monitored periodically by the DMC according to a pre-specified process and frequency detailed in the DMC charter.

In addition, a steering committee has been assigned to this trial. In case need arises, Ad hoc DMC meetings will be initiated by the steering committee.

Every effort will be made to reach a consensus within the Data Monitoring Committee and with the principal coordinating investigator. In case of disagreement on recommended modifications to the protocol, the Steering Committee will make the final decision.

Follow up data will be collected up to 3 years from PDE visit for all patients to evaluate long term safety and efficacy of the investigational product.

Number of Patients	74 patients
Planned trial period	FPI to Last Patient Out (LPO): Approximately 34 months;
Treatment and follow up duration per patient	**Total**: Approximately 14-16 months, per patient: 1-3 weeks screening period, 6 weeks treatment period, 5 weeks post-treatment to PDE, up to 12 months Follow Up (FU) period from the PDE including a maintenance therapy of a single instillation once monthly up to 11 months FU.
Trial population	Adults patients with LG, non-invasive UTUC in renal pelvis and calyces above the UPJ (Ureteropelvic Junction)
Inclusion Criteria:	1. Patient has signed Informed Consent Form and is willing and able to comply with all requirements of the protocol. 2. Patient is at least 18 years of age. 3. Naive or recurrent patients with LG, non-invasive UTUC in the pyelocalyceal system. 4. Patient has at least one (1) measurable papillary LG tumor, evaluated visually, ≤ 15 mm. The largest lesion should not exceed 15mm. 5. Biopsy taken from one or more tumors located above the ureteropelvic junction (UPJ) showing LG urothelial carcinoma. Diagnosed not more than 2 months prior to the screening. 6. Patient should have at least one remaining papillary LG tumor evaluated visually with a diameter of at least 5 mm. 7. Wash urine cytology sampled from the pyelocalyceal system

	documenting the absence of HG urothelial cancer, diagnosed not more than 2 months prior to the screening. 8. Patients with bilateral LG UTUC may be enrolled if at least one side meets the inclusion criteria for the trial and if the other kidney does not require further treatments (The other kidney can be treated prior to the beginning of the study).§ 9. Patients with ECOG (Eastern Cooperative Oncology Group) performance status <3 (with Karnofsky >40). 10. Patients with life expectancy greater than 24 months at time of screening. 11. Patients must have adequate organ and bone marrow function as determined by routine laboratory tests as below: Patients must have 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 × institutional ULN, and • Estimated glomerular filtration rate (eGFR) ≥30 mL/min. • In rare instances, the Principal Investigator may enroll patients whose laboratory screening values do not conform exactly to the levels outlined above but who, in the judgement of the local PI, the DMC and the coordinating PI can be safely and ethically treated on protocol. 12. Patient has no active urinary tract infection (UTI) as confirmed by urine culture or urinalysis*. 13. Female Patients of childbearing potential**, must have a negative serum pregnancy test at screening and must agree to use two acceptable & effective methods of contraception***, until 6 months post treatment. 14. All sexually active male patients must agree to use a condom during intercourse, for at least 48 hours post each instillation. 15. Male patients who have a partner that is a female of childbearing potential must agree to use two acceptable & effective methods of contraception until 6 months post treatment. 16. Patients must not have any other medical condition(s) that make(s) their participation in the study unadvisable in the opinion of the investigator. (§ *; **; ***; see end of Exclusion Criteria)
Exclusion	1. Patient received BCG treatment for UC during the 6 months prior to Visit 1.

Criteria:	2. The patient has untreated concurrent urothelial cancer in other locations other than the target area (unless treated during screening). 3. Carcinoma in situ (CIS) in the past in the urinary tract. 4. Patient has a history of invasive urothelial carcinoma during the past 5 (Five) years. 5. Patient has a history of high grade papillary urothelial carcinoma in the urinary tract during the past 2 (Two) years. 6. Patient is actively being treated or intends to be treated with systemic chemotherapy during the duration of the trial. 7. Any other malignancy diagnosed within 2 years of trial entry with the exception of: a. Basal or squamous cell skin cancers, or b. Noninvasive cancer of the cervix, or c. Any other cancer deemed to be of low-risk for progression or patient morbidity during trial period. 8. Patient with urinary obstruction in a case of retrograde administration or administration not feasible via nephrostomy tube. 9. Inability to deliver the investigational drug to the pyelocalyceal system. 10. Patient has any other medical or mental condition(s) that make(s) his/her participation in the trial unadvisable in the opinion of the treating urologist. 11. Patient has contraindication to MMC treatment, or known sensitivity to MMC. 12. Patient has an intractable bleeding disorder (e.g., coagulation factors deficiencies, Von Willebrand Disease). 13. Patient is currently receiving any other investigational agents or has participated in a research protocol involving administration of an investigational product within the past 30 days prior to Visit 1. 14. Patient previously treated with MitoGel™ for UTUC. 15. Pregnant (positive serum pregnancy test), planning to become pregnant during the trial period, breast-feeding, or of childbearing potential and not practicing reliable contraception***. 16. Patient is non-responder to Mitomycin C as a chemical ablation agent for urothelial carcinoma. This criterion relevant only to patient who already participated in another UroGen's studies or any other relevant studies with chemical ablation efficacy endpoint. § If both upper tracts meet inclusion criteria, the treating urologist in consultation with the sponsor can decide which side is to be treated within the trial. The other side should be treated as per standard of care, however if the other kidney treatment includes an intravesical instillations, the patient is not eligible. In any case, the other kidney must be free of cancer before the first instillation on the side to be treated in the clinical trial.

	* In case of a symptomatic UTI the patient will be treated with a full course of antibiotics, and the instillation will be postponed until resolution. In the case of asymptomatic bacteriuria, the use of prophylactic antibiotics and postponement of the treatment is left to the discretion of the PI. ** Women of non-childbearing potential: 1. At least 12 months since the last menses, or 2. Without uterus and/or both ovaries, or 3. Has been surgically sterile for at least 6 months prior to trial drug administration. *** Acceptable methods of birth control which are considered to have a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as implants, injectable, combined (estrogen/progesterone) oral contraceptives, intrauterine devices (IUDs-only hormonal), condoms with spermicide, sexual abstinence or vasectomized partner.
Statistical Methodology	Approximately 83 patients will be recruited to provide at least 74 evaluable patients. While no interim efficacy analysis is planned: • A futility analysis is planned after 20 subjects have reached PDE, • The DMC will periodically review safety and efficacy data and will, if appropriate, recommend earlier submission to FDA in the case where it has concluded that safety and efficacy have been demonstrated. If this were to occur, the study would nevertheless continue while FDA evaluates the data provided. **Sample Size Rationale**: A total of approximately 83 subjects are planned to provide at least 74 who are evaluable that will provide 88.5% power to demonstrate the hypothesized CR rate of 30% is higher than the performance goal of 15%. Power is estimated using an exact binomial hypothesis testing with two-sided Alpha=0.05.

	Primary Efficacy Analysis: The primary efficacy analysis will test the following hypotheses in ITT, using an exact binomial hypothesis testing: H_0: $CR_{rate} \leq 15\%$ H_1: $CR_{rate} > 15\%$ **Key Secondary Efficacy Analysis:** The key secondary efficacy analysis will test the following hypotheses in the CR analysis set of subjects demonstrating CR at PDE, using exact binomial testing: H_0: Durable CR at 12-months $\leq 40\%$ H_1: Durable CR at 12 months $> 40\%$ In addition, durability of CR will be analyzed continuously using Kaplan-Meier curve.
	Interim Analysis A futility analysis will be conducted after N = 20 evaluable subjects have provided primary efficacy data. Results of the analysis will be provided to the DMC. The DMC will forward its recommendations following DMC meetings to the steering committee, which will than make the final determination on trial continuation.

6. Key Roles and Contact Information

Sponsor

UroGen Pharma Ltd.
9 Ha'Ta'asiya., POB 2397
Ra'anana, 4365405, Israel
info@urogen.com
Tel: +972-9-770-7600
Fax: +972-77-4171410

Trial Manager

Ifat Klein, Ph.D.
Director of clinical development and operations, UroGen
sponsor@urogen.com

Medical Monitor / Pharmacovigilance Officer

Michal Jeshurun, MD, UroGen
safety@urogen.com

Medical Director

Mark P. Schoenberg, M.D, UroGen
safety@urogen.com

Quality Assurance

Gilad Bernadsky
VP, Quality Assurance, Urogen
qa@urogen.com

Principal Coordinating Investigator

Dr. Seth Paul Lerner
Site: Baylor College of Medicine M.C.
Houston, Texas 77030, USA
slerner@bcm.edu
Office Phone: (713)798-6841

Data Management & Statistics

TechnoSTAT Ltd
34 Jerusalem Rd.
Ra'anana, 4350108, Israel
info@technostat.co.il
Tel:+972-9-7669333

Primary Central Pathology and Cytology Reviewer

Mahul Amin, MD
Department of Pathology and Laboratory Medicine,
University of Tennessee Health Sciences Center,
930 Madison Avenue, 5th floor
Memphis, TN, 38163
Phone: 901-448-7020

Secondary Central Pathology and Cytology Reviewer

Secondary central lab Address
Attn.: Dr. Guliz Barkan
Department of Pathology
Loyola University Hospital
GBARKAN@lumc.edu
EMS Building, Room 2238
2160 S 1st Ave, Maywood, IL 60153
Phone: 708-327-2081
Fax: 708-327-2620

Pharmacokinetics Central Lab

AIT Bioscience
7840 Innovation Blvd
Indianapolis, Indiana 46278, USA
Tel: (317)-715-8800

Study Logistics:

Dima Zolotaryov, UroGen
logistics@urogen.com

7. Introduction and Background

7.1. Upper tract urothelial carcinoma (UTUC)

Upper tract urothelial carcinomas (UTUCs) are malignant changes of the transitional urothelial cells lining of the upper urinary tract. UTUC are uncommon and account for only 5%–10% of urothelial carcinomas (UCs) [Browne, 2005; Rouprêt, 2013; Hurwitz, 2014], and the estimated annual incidence of UTUCs in western countries is about two new cases per 100,000 inhabitants. UTUC is found in the renal pelvis (in about two-thirds of the cases) and the ureter (in about one-third of the cases) [Jarrard, 2012]. Concurrent bladder cancer is present in approximately 17% of cases of UTUC. In 22%–47% of UTUC patients, recurrence occurs in the bladder, whereas recurrence in the contralateral upper tract is observed in 2%–6% [Rouprêt, 2013].

About 60% of UTUCs are invasive at diagnosis, with a peak incidence in people in their 70s and 80s, and prevalence is 3 times higher in men than in women. [Rouprêt, 2013].

The most common symptom of UTUC is microscopic or gross hematuria (70%–80%), while flank pain occurs in 20%–40% of cases, and a lumbar mass is present in 10%–20% [Hall, 1998: Rouprêt, 2013].

Screening and diagnosis of UTUC consists of upper tract urinary cytology, various imaging assessment methods, and ureteroscopy [Grossfeld, 2001, Rouprêt, 2013, Hurwitz 2014]. Urinary cytology correlates with the presence of urothelial carcinoma, but does not accurately predict the stage or grade of these respective tumors [Messer, 2011; Sverrisson, 2014]. Flexible ureteroscopy can assess the tumor, obtain tumor biopsy, and determine tumor grade in 95% of cases [Tavora, 2009; Rouprêt, 2013]. Multi-Detector Computed Tomographic Urography (MDCTU) is the gold standard for exploration of the upper urinary tract and has high sensitivity in the detection of small renal lesions [Scolieri, 2000].

7.2. Current treatment:

7.2.1. Surgical treatment

Radical nephro-ureterectomy (RNU) with excision of bladder cuff (through either open or laparoscopic access) is the gold standard of care for upper tract urothelial cancer in patients with a normally functioning contralateral kidney [Lughezzani, 2010; Rouprêt, 2011; Cutress, 2012; Rouprêt, 2013]. RNU is indicated in cases of:

- Upper ureteral and renal pelvic tumors,

- Infiltrating tumor on imaging,
- High-grade tumor, and
- Multifocality (with two functional kidneys).

7.2.2. Nephron-Sparing Procedures (NSP)

Conservative surgery, or first-line nephron-sparing procedures (NSP) for low-risk UTUCs allows preservation of the upper urinary and renal unit while sparing the patient the morbidity associated with open radical surgery. Conservative management of UTUCs can be considered in imperative cases (renal insufficiency or solitary functional kidney) or in elective cases (when the contralateral kidney is functional) for LG, low-stage tumors [O'Malley, 2009; Volanis, 2012; Cutress, 2012; Rouprêt, 2014]. Combining ureteroscopic biopsy grade, diagnostic imaging findings, and urinary cytology may help decision making on radical RNU versus NSP [Rouprêt, 2011; Rouprêt, 2014]. Recent recommendations have established selection criteria for NSP (i.e., LG biopsy, unifocal tumor <1 cm in diameter, complete resection possible, no evidence of parenchymal invasion on imagery, patients informed of and committed to the need for closer surveillance). Advances in imaging techniques, practice of systematic ureteroscopic biopsies, and development of preoperative prediction tools also allow for a better selection of candidates who would benefit from NSP [Colin, 2013]. Disease recurrence has been shown to be common after NSP (ranging between 26%–90%), which mandates a regular, close, lifelong follow-up of the upper urinary tract [Pak, 2009; Cutress, 2012; Colin, 2013; Kalaitzis, 2013]. The challenge of high recurrence rate and the (low) potential for progression following NSP often requires patients to undergo multiple resection procedures. Thus, in addition to clinical characteristics, the motivation, comprehension, and compliance of the patients are required [Cutress, 2012; Colin, 2013; Kalaitzis, 2013; Rouprêt, 2007; Rouprêt, 2013]. Nevertheless, as clinical stage and tumor grade are prognostic factors for recurrence and survival [Rouprêt, 2007], choosing the correct patient population for this treatment will increase the chances of treatment success and reduce the risk.

In a retrospective review of a cohort of 57 patients treated conservatively and followed for a minimum of 2 years, the recurrence rate was 89.5%, with a mean of 5.5 recurrences per patient [Pak, 2009; Park, 2013). The average number of procedures per patient was 10.1, over a range of 5 to 41 months. The most conservative estimate of overall survival for UTUC treated with the current paradigm is 35%, for a cohort with an average age of 74 years with 35 months

of follow-up, with progression of the UTUC as the cause of death in approximately 50% of the patients [Krambeck, 2007). There are few reports that have evaluated the quality of life (QOL) in patients with UTUC, but it is apparent that patients with non-muscle invasive bladder cancer who were undergoing repeated transurethral resections had lower general health perceptions than normal cohorts [Yoshimura, 2005). It seems that in patients with LG, small-sized tumors have equal endpoints following endoscopic treatment as compared to RNU, with the advantages of minimal morbidity and preservation of renal parenchyma following endoscopic management [Singh, 2011; Rouprêt, 2013]. To date, however, only a few studies have reported long-term endpoints after NSP in UTUCs and strong data are lacking to assess definitively the cancer control allowed by this therapeutic strategy [Colin, 2013]. As it seems that a tumor-free status can be achieved only rarely, therapy for urothelial cancer in the upper urinary tract represents a significant unmet medical need [Volanis, 2012; Grasso, 2012; Kalaitzis, 2013].

7.2.3. Chemotherapy

Transitional cell tumors of both the upper and lower urinary tract are considered to be chemo-sensitive tumors. Intravesical Mitomycin C (MMC) therapy for lower urinary tract (bladder) transitional cell carcinoma has been used for more than two decades, as adjuvant therapy. Its use in upper tract (renal pelvis and ureter) transitional cell carcinoma has showed promise in terms of both efficacy and safety, but the number of published studies is limited, due to low incidence and prevalence of this type of tumor [Keeley, 1997].

A variety of adjuvant topical chemotherapy studies demonstrated ability to reduce the risk of tumor recurrence in the UUT and in the bladder following UTUC operative treatments (both RNU and NSP). The optimal use of adjuvant chemotherapy, using MMC, Bacillus Calmette-Guérin vaccine (BCG), or cisplatin, is not defined yet [Elliott, 1996; Martinez-Pineiro, 1996; Sakamoto, 2001; Matin, 2010; O'brien, 2011; Kim, 2013; Rouprêt, 2013]. In addition, only a few neo-adjuvant systemic chemotherapy studies have been published to date, and they demonstrated some complete response (chemical ablation), a significant rate of down-staging, and significantly higher survival rates than surgery without neo-adjuvant chemotherapy [Matin 2010, Rouprêt 2013, Porten 2014]. Thus, the cumulative data provide justification for the additional clinical trials using improved adjuvant and neo-adjuvant chemotherapy strategies [Rouprêt, 2013; Audenet, 2013b].

Difficulties in administering and maintaining MMC or other topical chemotherapeutic agents for sufficient time to the upper tract have limited their use for chemo-ablative purpose in

patients with UTUC [O'Donoghue, 2004]. The improved efficacy of MMC following the increase in exposure time was established by numerous *in-vitro* models, *in-vivo* clinical studies, and computer simulations [De Bruijn, 1992; Sadeghi, 1998; Au, 2002]. Therefore, providing a means to prolong the duration of MMC intravesical treatment is imperative for enhancing the anti-tumor effect of the instilled MMC.

Mitomycin C is inactivated by acid urine (Au et al. 2001). Therefore, the patients in this study will receive 1.3 gr of sodium bicarbonate 3 times prior to every instillation for alkalization of urine.

7.3. Investigational Product: MitoGel™ (TC-3 and MMC)

The investigational product is presented in MitoGel™ Kit comprising MMC for injection drug product (the active component), and TC-3 Sterile Hydrogel.

MitoGel™ is initially prepared as a cooled liquid preparation; as a reverse thermal hydrogel, MitoGel™ subsequently solidifies at body temperature at the site of instillation in vivo, leading to the formation of a MMC containing gel-depot. As a result, the MitoGel™ provides prolonged exposure of UTUC tumors to MMC. Accordingly, MitoGel™ is envisioned to act as a chemoablative therapeutic product in the setting of UTUC. Studies reported in the literature indicate a direct correlation between anti-tumor activity and instilled MMC concentration and dwelling (exposure) time on treatment effectiveness [Deb, 2001; Eastham, 1993; Schmittgen, 1991; Wang, 2013].

Prolongation of the MMC exposure time is expected to increase the drug efficacy over time while maintaining similar or lower systemic peak exposure, and therefore a good safety profile is expected. *In-vitro* models, *in-vivo* studies, clinical trials, and computer simulations have shown that enhancement of MMC activity may be achieved by increasing MMC dwelling time and drug concentration in the target tissue [Barlogie, 1980; De Bruijn, 1992; Nozue, 1995; Ozawa, 1998; Perry, 1992; Sadeghi, 1998; Schmittgen, 1991; Slee, 1986; Walker, 1986].

Furthermore, owing to the nature of the TC-3 component of the MitoGel™, mixing with the drug and instillation via a standard ureteral catheter is relatively straightforward, as the unique thermo-sensitive properties enable it to convert from a liquid state when chilled, throughout the mixing with the drug and the instillation, into a semi-solid gel at body temperature inside the target organ.

Following instillation of MitoGel™, MMC is efficiently released from TC-3 when the gel is dissolved by the urine [TheraCoat, 2014a, Report No. TAS-4M-P-A-133, Rev 3]. Preliminary studies provide in-vitro and in-vivo data that support the use of this formulation of sustained-release MMC. The release profile of MMC from MitoGel™ was evaluated in in-vitro studies. A linear release of MMC was observed from MitoGel™ for up to eight hours, with more than 90% release achieved after 10 hours, supporting the assertion that MMC is mainly released from the gel once the gel dissolves. The results of safety and performance tests reveal that TC-3 is biocompatible, poses no deleterious effect on the urothelium and does not obstruct ureters or urethra upon instillation and the subsequent solidification of the gel.

Preclinical studies in swine demonstrating low MMC plasma levels, well below the toxicity level, support the systemic safety of upper-tract instillation of MitoGel™. In a GLP toxicology study (MPI # 2189-007), six weekly instillations of 7 mL MitoGel™ to the upper urinary tract of domestic pigs at a total MMC dose of up to 56 mg MMC (concentration of 8 mg/mL) were not associated with any mortality, clinical findings, changes in body weights, ECG intervals or meaningful changes hematologic, coagulation, serum chemistry , urinalysis or urine chemistry endpoints, at any collection interval, up to and including the 4 weeks recovery period at the end of the instillation period.

Analysis of plasma samples found that following retrograde instillation of MitoGel™, systemic exposure ($AUC_{0\text{-}10hr}$) and C_{max} values of MMC increased with increasing dose in an approximately dose proportional manner on Days 1 (1^{st} instillation) and 36 (last instillation). It should be noted that systemic exposure levels were significantly below report levels known to cause myelosuppression (threshold of 400 ng/mL).

Macroscopic findings in the ureter of mild to moderate swelling/thickening and/or irregular surface were noted at necropsy following the last instillation in a dose dependent pattern. These corresponded to microscopic findings of edema and/or urothelial vacuolation. Four weeks following the last instillation, findings of mild swelling/thickening of the ureter were rare.

Microscopic findings noted in the kidney were confined to the pelvis, involving the urothelium and submucosa. These findings included urothelial vacuolation, urothelial hypertrophy, and erosion; while edema, mixed leukocyte infiltrates, and hemorrhage were primarily found in the submucosa. Similar microscopic findings were noted mostly in the proximal ureter. The findings were similar in nature to the findings described in the literature

for intravesicular MMC treatment. Microscopic findings trended towards resolution over the recovery period, with decreased severity and incidence after the recovery phase. The microscopic findings were considered to be non-adverse, given the generally limited severity, the progression towards recovery, the lack of associated clinical or clinical pathology findings, the lack of systemic changes, and the localized nature of the microscopic findings.

Based upon the results of this study, six weekly repeated administrations of MitoGel at a concentration of 8 mg/mL (56 mg MMC) was found to produce no adverse effects. Taken together, TC-3 Sterile Hydrogel appears to provide a safe drug retention and delivery system for MMC in the upper urinary tract.

While MMC has been studied extensively and is routinely used in clinical practice for intracavital (as well as systemic) administration, the human experience with MitoGel™ is limited. As of July 2016, MitoGel™ has been used as compassionate use treatment in 18 patients for whom the remaining treatment alternative was removal of the affected kidney. Out of 18 recruited patients, 14 were classified as LG. To date, of the 14 LG UTUC patients (our target patient population for the pivotal trial), we noticed the following results:

- Eleven patients completed the 6 weekly instillations (the anticipated protocol in the planned pivotal trial)
- 10 patients were evaluable (one patient was only partially evaluable)
- Of these 10 patients, all patients have responded; 7 having reported complete responses (CR) and 3 with partial responses (PR)
- 2 out of the 3 PR's were treated with low MMC concentration formulation of MitoGel
- Response durability evaluation is ongoing and encouraging

The most commonly reported adverse events by patients was flank pain (n=6) or "fullness" sensation (5 patients) during the instillation procedure or during the period immediately following the instillation. These adverse events are believed to be associated with the instillation of the gel or insertion of the ureter catheter, and were generally mild or moderate and resolved without treatment. Three patients had acute Pyelonephritis (one of them with aggravation of chronic renal failure) which resolved following IV antibiotics. This event is a known and accepted AE in cases of upper tract manipulations. Other events reported which are believed to be related, or partially related to the MMC component of the investigational product is allergic reaction to Mitomycin, involving palmar and arm rash and pruritus (n=1), and cheek blush and swelling (n=1) and post instillation short single or recurrent febrile event (n=3),

Nausea was reported in four patients and can be related either to upper tract manipulations or to MMC itself. In addition, pancytopenia was evident in two patients: The first being an elderly previously polycythemic patient who received Hydrae (a myelosuppressant) concomitantly with the investigational product and the second patient underwent the following in the same treatment session: TURBT, immediate MMC instillation to the bladder and upper tract instillation with MitoGel which probably led to enhanced systemic absorption of MMC. Weakness, fatigue and dizziness could also be related to MMC component of MitoGel as well as a single case of bladder inflammation and upper tract inflammation. Both of which completely resolved.

MMC mixed with TC-3 has also been studied as an ablative intravesical treatment in Non-Muscle Invasive Bladder Cancer (NMIBC). While the different anatomy of the UUT may pose new challenges, the clinical data from the bladder instillations is relevant to support safety and efficacy of MMC in the upper tract, as it consists of a similar epithelial tissue and can provide some information with regard to the expected adverse events

7.4. Justification of Trial Design

The present trial is designed to evaluate the efficacy and safety of MitoGel™ administered to the UUT in patients with LG-UTUC.

Only a few trials were performed with chemotherapy and endoscopic management in UTUC, and the trials differed one from each other in eligibility criteria, treatment specificities and results [Cutress, 2012; Ristau, 2012; Audenet, 2013a]. However, it can be collectively concluded that favorable population that benefit from elective endoscopic management have non-invasive LG disease characteristics [Cutress, 2012; Rouprêt, 2013]. Therefore, we chose to have naive or recurrent patients with LG, non-invasive UTUC, as the target population for this trial.

There are only few publications on instillation of MMC as either adjuvant or neo-adjuvant therapy in the upper urinary tract [Hellenthal, 2009; O'Brien, 2011]. In the literature, the total dose for MMC instillation in the UUT ranges from 20 to 60 mg (with concentrations generally ranging from 1-2 mg/mL) [Keeley, 1997; Nepple, 2009; Aboumarzouk, 2013; Wang, 2013; Hurwitz, 2014].

More data is available on instillation of MMC as adjuvant therapy for urothelial cancer of the bladder. Given the similarity of the disease and urothelial lining throughout the urinary

tract, the experience with MMC in the bladder is informative and can be used to determine the concentration of instillation in the UUT.

The FDA has granted an orphan designation for MitoGel for "treatment of upper tract urothelial carcinoma (UTUC)". To date, UroGen have conducted over 250 instillations in the upper tract of 42 swine, at three dose concentrations i.e., 2mg, 4mg and 8mg per mL, of the product in a GLP toxicology study evaluating the safety of the MitoGel™, simulating the intended regimen in the clinic at higher concentration, with each swine undergo 6 weekly instillations. This GLP regulated toxicity study was conducted in support of the IND submission to the agency.

The study concluded that even at the high concentration used, which are double than the one proposed in the clinical settings (8mg of MMC per mL of gel in the GLP study vs. 4mg of MMC per mL of gel in the human study) no toxicity has been observed (systemic or local).

The dose selected for the UTUC patients in the phase 3 study is 4mg of MMC per mL of gel, to allow a safety margin, which was accepted by the FDA during pre-IND discussions.

This safety data together with the clinical experience of using MitoGel™ in human subjects (over 60 instillations in 18 subjects collected from the Expanded Access Program) was found acceptable by the FDA in order to move forward with this study.

In the current trial, the total dose to be instilled in patients will not exceed 60 mg MMC. The concentration of MMC in MitoGel™ will be 4 mg MMC/1 mL TC-3. This is similar to the dosage of MMC used for intravesical instillations and in post/peri-operative instillations in the UUT [Mohamed, 2011 (Smith's Textbook of Endourology, 2011 see page 291)]. Due to the inter-individual variability in the anatomy and volume of renal pelvis and calyces, the volume of the MitoGel™ for the instillation will be determined for each patient individually by the investigator. This will be based on volumetric estimation using retrograde pyelography for injecting the contrast agent (maximal volume required to fill the pyelocalyceal space). Based on clinical experience from the Expanded Access Program treatment in UTUC patients, it is estimated that between 5 and 15 mL of MitoGel™ should be sufficient for filling and even distribution of the gel within the renal pelvis and calyces.

7.4.1. Justification of single arm

This treatment protocol addresses an unmet medical need for an orphan indication. The standard treatment for UTUC requires either nephroureterectomy or endoscopic surgical

resection. In this protocol the utilizing of a primarily non-surgical approach to the management of UTUC is explored. In pre-IND discussions, the FDA has agreed with the single arm design of this trial. There is no comparable non-surgical "ablative" therapy to which MitoGel™ can be compared. In addition, MitoGel™ is indicated as a nephron sparing approach for patients who are currently candidates for RNU, therefore, neither equivalent control nor placebo arms are applicable or may be considered due to unethical reasons.

7.4.2. Justification of the trial primary endpoint

The primary efficacy endpoint is the rate of complete response (CR); i.e., a complete ablation of tumor lesions as a response to the chemotherapy treatment, which will be assessed during the primary disease evaluation (PDE) Visit. The PDE will occur at the pre-scheduled visit for endoscopic management treatment, set for 5 weeks following the last instillation (altogether, approximately 3 months from baseline). As tumors are not expected to disappear spontaneously, response can be attributed to the treatment, making the rate of CR an appropriate endpoint for a trial lacking a placebo control arm. For confirmation of therapeutic benefit, durability of ablation at 3 months post PDE has been chosen as a secondary endpoint. This time-point was chosen because recurrence within 3 months post-surgical removal of bladder lesions has been previously associated with the efficiency of the surgical procedure indicative of incomplete removal of the lesions rather than true recurrence. Therefore, a "second look" (clinical evaluation) at 3 months post Transurethral Resection of Bladder Tumor (TURBT), for example, is recommended in the guidelines [Kapoor, 2013; Rouprêt, 2013]. Durable CR at Month 3 post PDE in this trial will be taken to indicate a complete ablation of the tumor(s) and is thus expected to be indicative of the efficiency of the new treatment offered and a confirmation of efficacy. Accumulating evidence of recurrence rate and of time for recurrence post retrograde management varies significantly between different publications [Kapoor, 2013; Rouprêt, 2013]. In this trial, we will follow recurrence rate and time for 12 months post PDE, as exploratory endpoints.

7.5. Potential Risks and Benefits

7.5.1. Potential risks

Toxicity associated with systemic absorption

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 renal toxicity are considered possible risks for the patients. The CBC, renal, and liver blood function will be checked regularly during the trial.

Allergic Response to MMC

MMC (Kyowa) bladder instillations have been shown to cause allergic reactions in various toxicities 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. Allergic response will be closely monitored during the trial.

Cystitis

Cystitis and other bladder irritation symptoms secondary to UUT instillation of MMC may develop. Urine tests, including urine culture and urinalysis, will be checked regularly during the trial.

UTI and Pyelonephritis

Aiming to minimize the risk for Urinary Tract Infections (UTI), especially Acute Pyelonephritis, anti-microbial prophylaxis should be prescribed according to the AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (See Appendix VI);

Onset of renal insufficiency or deterioration of renal function

Although uncommon, treatment may cause impairment of renal function. Renal functions test will be checked regularly during the trial.

7.5.2. Potential benefits

This trial is potentially beneficial in several aspects:

- It will evaluate a new mode of UTUC treatment, MitoGel™ for local therapy, that may prevail the drawbacks of the current UTUC topical treatment,
- It may entail good safety profile of MitoGel™ in UTUC patients.

8. Trial Objectives

8.1. Safety

- To evaluate the safety and tolerability of the MitoGel™ Admixture in UTUC patients.
- To assess the pharmacokinetics profile of Mitomycin C (MMC) in plasma of a sub-group of patients treated with MitoGel™ Admixture.

8.2. Primary Efficacy

- To evaluate the tumor ablative effect of MitoGel™ Admixture in UTUC patients at PDE visit.

8.3. Key Secondary Efficacy

- To evaluate response durability at 12-months follow-up for subjects showing CR at PDE visit

8.4. Secondary Efficacy

- To evaluate the durability of tumor ablative effect of MitoGel™ Admixture in patients who demonstrated complete response (CR) at the Primary Disease Evaluation (PDE) Visit, 3, 6 and 9 months following the PDE visit.
- To evaluate the overall clinical benefit to treatment with MitoGel™ admixture

9. Trial Endpoints

9.1. Safety Endpoints

Study's safety endpoints include:

- Adverse events and serious adverse events occurring at any time during the study,
- Laboratory tests,
- Physical and urology oriented examinations,
- Vital signs.

In addition, pharmacokinetic (PK) profile of the first MMC instillation in the blood will be examined for the first six patients.

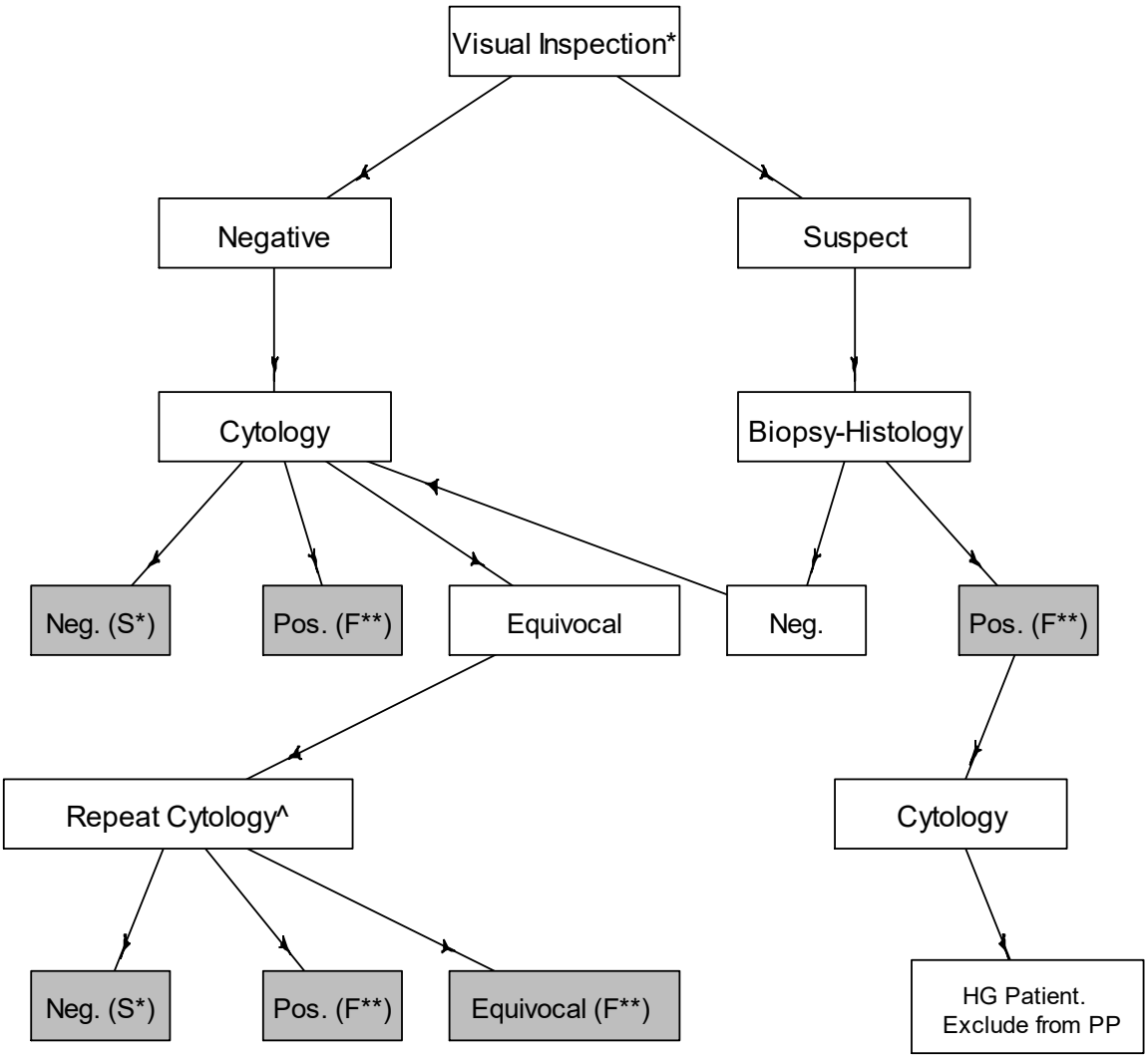
9.2. Efficacy Endpoints

9.2.1. Primary Efficacy Endpoint

Study's primary endpoint is Complete Response (CR) at the end of the treatment period (PDE Visit). CR is defined dichotomously as "Success" if CR was confirmed at PDE visit (or relevant follow-up; see Figure 1 below), and "Failure" otherwise.

There are a number of diagnostic scenarios for CR, which are described in the following figure.

Figure 1: Method for Determining Complete Response



Gray boxes present final outcome
S* = Success
F** = Failure
^ = repeat cytology at 13 weeks, when subject returns for first post PDE instillation

9.2.2. Key Secondary Efficacy Endpoint

Long Term Durability of CR: This endpoint is defined only for those patients demonstrating CR at PDE visit. The endpoint is defined dichotomously as "Success" if CR was obtained at follow-up Visit 4 (12 months post PDE visit), and "Failure" otherwise.

9.2.3. Secondary Efficacy Endpoints

- Durability of CR defined dichotomously as "Success" if CR was achieved at PDE visit and remained at follow-up Visit 1, Visit 2 and Visit 3 (3, 6 and 9 months post PDE visit), and "Failure" otherwise.
  This endpoint is defined only for those patients demonstrating CR at PDE visit.
- Partial response at PDE visit will be defined dichotomously, similarly to the primary efficacy endpoint. For subjects with partial response at PDE visit, originally planned and actual treatments will be compared.

9.3. Trial Design

The current trial is a prospective, open-label, single-arm phase III trial, designed to assess efficacy tolerability and safety of MitoGel™ treatment administered to the upper urinary tract.

Upon signing of informed consent, the patients will undergo a screening visit for eligibility evaluation. Eligible patients with confirmed LG non-invasive UTUC will be treated with 6 once-weekly instillations of MitoGel™ in a retrograde fashion. Instillation through a nephrostomy tube may be an option, if necessary upon advising with the principle coordinating investigator.

Determination of the eligibility of the entire patients and admission into the trial will be decided upon a case-by-case basis in consultation with the trial principle coordinating investigator (Dr. Seth Lerner). Patient relevant data will be sent by email to the Sponsor and images will be uploaded to a secure portal (AG MedNet). The patient's medical history, concomitant medications, pyelography imaging of the pyelocalyceal system anatomy, URS photos when available, local pathology and cytology results and all other relevant clinical records will be sent in un-identified manner. **The entire patient information should be sent to the Sponsor no later than 7 working days from the screening visit and earlier if possible**. The final eligibility will be approved by email from the sponsor to the site.

MitoGel™ Admixture concentration to be used in this trial will be 4mg MMC per 1mL of TC-3 gel.

The volume of the MitoGel™ Admixture to be instilled will be individualized, based on the volumetric estimation of the pyelocalyceal space using retrograde (antegrade if required) pyelography. To increase accuracy, an average of three (3) measurements will be the reference in case the number contains decimal fraction it should be round to the closest whole number.

The pyelography procedure can be done at any time before the first instillation and in accordance with the method of administration selected by the investigator. The measurements will be documented in each patient's study file and the volume required to fill the UUT will be recorded.

Prior to every instillation, the treating investigator/designee must review the pyelocalyceal volume measurement recorded in the patient file and complete the designated MitoGel administration form which is provided by UroGen, with the required volume for instillation. The volume will be verified by site team observer. Both treating urologist and the observer will sign the administration form, thus confirming the correct volume will be instilled.

Thereafter, the treating investigator/designee will withdraw the exact volume required into the syringe.

Once instillation is completed, the investigator /designee who performed the instillation will complete the actual volume instilled and sign the administration form. The administration form will be filed in the study patient file. These steps will be repeated at each administration.

Administration of MitoGel™ Admixture to the upper urinary tract shall be carried out while the patient is in Trendelenburg position and lies down on the side that is being treated to the extent that it is possible.

Patients should remain in the clinic/hospital for at least 6 hours observation period following the first instillation procedure.

Placement of a ureteral catheter for instillation of MitoGel™ should be performed as follow: 1. Cystoscopy should be performed in order to obtain screening of the urethra and the bladder for abnormal findings, 2. advance guidewire through the cystoscope working channel via the ureter to the renal pelvis, 3. anchor the guidewire in the renal pelvis and remove the cystoscope, 4. advance the ureteral catheter over the guidewire to the preferable location in the renal pelvis and take photos to document the location of the catheter tip. Preferable location will be considered as the place where the flow from the catheter tip of the investigational product will enable best coverage of MitoGel™ in the renal pelvis and the calyces. Fluoroscopy should be used to ensure proper placement of the catheter within the renal pelvis prior to instillation.

The ablative effect of the MitoGel™ will be evaluated at the pre-scheduled ureteroscopy (URS) (on PDE visit), performed 5 weeks after the last instillation. Response will be

determined based on upper tract wash urine cytology followed by visual evaluation using video-ureteroscopy (appearance, number, size, and location of the lesions), and histopathology of remaining lesions. A biopsy shall be performed for all remaining lesions where it is technically feasible. Cytology and histophathology slides will be reviewed by the local and the central pathology lab. The determination of degree of response and durability of complete response for trial analysis purposes will be based on the local lab readings.

An independent Data Monitoring Committee (DMC) is assigned for this trial. Accumulated safety, tolerability, and efficacy data will be monitored periodically by the DMC according to the schedule and scope defined in the DMC charter. The DMC is established according to the FDA's Guidance (Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees; 2006).

A trial steering committee is also assigned for this trial. In case of need the steering committee will initiate Ad hoc DMC meetings, and will review the DMC recommendations.

A futility analysis will be conducted after N = 20 evaluable subjects have provided primary efficacy data. Results of the analysis will be provided to the data monitoring committee (DMC). The DMC will forward to the steering committee its recommendations and the steering committee will make the final determination regarding trial continuation. The accumulated study data at this stage will be shared with the FDA for the decision of study continuation and/or adaptation. Study will continue to enroll subjects as per study plan while discussions Agency is taking place.

Safety will be determined based on physical examination, blood tests, vital signs, and a record of AEs. Any unexpected AE related to MitoGel™ and qualified per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) as grade 3 or 4 will be evaluated by the sponsor medical team and steering committee, see AE grading terminology in Appendix VIII: CTACAE 4.03 Severity Grades, and Allergic Reaction Grades.

9.4. Evaluation plan at PDE

Tumor response to treatment will be evaluated during the PDE visit occurring 5 weeks after the last treatment. Please refer to Section 15 for a detailed description of response evaluation criteria:

- Complete Response (CR) is defined as No Detectable Disease (NDD) and will be assessed visually during ureteroscopy (URS) and by upper tract washing urine cytology.

9.4.1. CR Patients Maintenance Instillations (Maintenance Visits)

- A maintenance treatment will start immediately after the local lab confirms that patient's cytology is negative for cancer, and no longer than 2-3 weeks post PDE, unless there is a medical condition which require to postpone the treatment. In these cases, the first maintenance instillation should be delayed until recovery.
- Maintenance Regimen- MitoGel™ Admixture will be given once monthly (±2 week) until one month prior to last FU visit within the study (i.e., until Month 11 post PDE).
- Safety assessment – During maintenance treatment at each instillation the patients will have performed in the hospital local lab, safety lab tests, physical examination and vital signs per protocol (see Appendix I - Appendix III). For patients who drop out of the study safety will be assessed according to the SOC.

9.5. Evaluation plan at follow-up

- Patients will be followed-up for twelve months (12) or until disease recurrent or progression.
- Patient will be given the maintenance treatment with the study IP during the follow-up period, meaning that the same safety assessment will be done as written in the above section.
- Three (3) months after PDE, the first follow-up (FU) visit will be conducted. During this visit, follow-up data on disease outcome will be collected.
- Additional follow-up data on disease outcome will be collected for up to 12 months after PDE.
- **Follow up data may be collected up to 3 years from PDE visit for all patients to evaluate long term safety and efficacy of the investigational product.**
- Disease outcome to be recorded will include the following:
  - Recurrence.
  - Progression defined as either change in stage according to the Tumor-Node-Metastases (TNM) classification, or grade according to the 2004 WHO classification of tumors.
- Any intervention conducted to treat the UTUC will be recorded.
- AEs will be recorded according to the rules described in Section 19.

9.6. Central Lab Pathologist

Biopsy and UUT cytology slides will be sent to the central lab pathologist at the screening visit. Biopsy slides from PDE and FU visits will be sent to the central lab pathologist according to the findings of this visit. Cytology slides will be sent to the central lab in any of the above visits.

9.6.1. General Process & Timelines

In case of low grade patient by local pathologist, and confirmation of eligibility by the investigator, biopsy and cytology slides should be shipped to the central lab no longer than 14 working days following the screening visit and after the site has received the eligibility confirmation by the Sponsor.

Central lab results are expected to be emailed to the site and UroGen within no longer than 4 working days.

The central lab should send the slides back to the site within 3 weeks of receipt.

In case of contradiction between local diagnosis and central lab diagnosis, here are the steps to be taken:

1. ***Study coordinator to forward the central lab report to the local pathologist requesting repeated review.***
2. ***Central lab findings provided to both physician and local pathologist***
3. ***Any change in physician diagnosis or treatment as a result of central lab findings will be recorded. At the same time, primary analysis will be based on initial determination based on site's local lab.***

In any case it is at the local PI judgment if to treat the patient within the study

10. Trial Population and Eligibility Criteria

Patients with LG, non-invasive UTUC lesions in the renal pelvis and calyces above the UPJ as determined by local lab.

10.1. Inclusion Criteria

1. Patient has signed Informed Consent Form and is willing and able to comply with all requirements of the protocol.
2. Patient is at least 18 years of age.
3. Naive or recurrent patients with LG, non-invasive UTUC in the pyelocalyceal system.

4. Patient has at least one (1) measurable papillary LG tumor, evaluated visually, ≤ 15 mm. The largest lesion should not exceed 15mm.
5. Biopsy taken from one or more tumors located above the ureteropelvic junction (UPJ) showing LG urothelial carcinoma. Diagnosed not more than 2 months prior to the screening.
6. Patient should have at least one remaining papillary LG tumor evaluated visually with a diameter of at least 5 mm.
7. Wash urine cytology sampled from the pyelocalyceal system documenting the absence of HG urothelial cancer, diagnosed not more than 2 months prior to the screening
8. Patients with bilateral LG UTUC may be enrolled if at least one side meets the inclusion criteria for the trial and if the other kidney does not require further treatments (The other kidney can be treated prior to the beginning of the study).§
9. Patients with ECOG (Eastern Cooperative Oncology Group) performance status <3 (with Karnofsky >40).
10. Patients with life expectancy greater than 24 months at time of screening.
11. Patients must have 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 × institutional ULN,
    - Estimated glomerular filtration rate (eGFR) ≥30 mL/min, and
    - In rare instances, the Principal Investigator may enroll patients whose laboratory screening values do not conform exactly to the levels outlined above but who, in the judgement of the local PI, the DMC and the coordinating PI, can be safely and ethically treated on protocol.
12. Patient has no active urinary tract infection (UTI) as confirmed by urine culture or urinalysis*.
13. Female Patients of childbearing potential**, must have a negative serum pregnancy test at screening and must agree to use two acceptable & effective methods of contraception***, until 6 months post treatment.

14. All sexually active male patients must agree to use a condom during intercourse, for at least 48 hours post each instillation.
15. Male patients who have a partner that is a female of childbearing potential must agree to use two acceptable & effective methods of contraception until 6 months post treatment.
16. Patients must not have any other medical condition(s) that make(s) their participation in the study unadvisable in the opinion of the investigator.

(§ *; **; ***; see end of Exclusion Criteria)

10.2. Exclusion Criteria

1. Patient received BCG treatment for UC during the 6 months prior to Visit 1.
2. The patient has untreated concurrent urothelial cancer in other locations other than the target area (unless treated during screening)
3. Carcinoma in situ (CIS) in the past in the urinary tract.
4. Patient has a history of invasive urothelial carcinoma during the past 5 (Five) years.
5. Patient has a history of high grade papillary urothelial carcinoma in the urinary tract during the past 2 (Two) years.
6. Patient is actively being treated or intends to be treated with systemic chemotherapy during the duration of the trial.
7. Any other malignancy diagnosed within 2 years of trial entry with the exception of:
   a. Basal or squamous cell skin cancers, or
   b. Noninvasive cancer of the cervix, or
   c. Any other cancer deemed to be of low-risk for progression or patient morbidity during trial period.
8. Patient with urinary obstruction in a case of retrograde administration or administration not feasible via nephrostomy tube.
9. Inability to deliver the investigational drug to the pyelocalyceal system.
10. Patient has any other medical or mental condition(s) that make(s) his/her participation in the trial unadvisable in the opinion of the treating urologist.
11. Patient has contraindication to MMC treatment, or known sensitivity to MMC
12. Patient has an intractable bleeding disorder (e.g., coagulation factors deficiencies, Von Willebrand Disease).

13. Patient is currently receiving any other investigational agents or has participated in a research protocol involving administration of an investigational product within the past 30 days prior to Visit 1.
14. Patient previously treated with MitoGel™ for UTUC.
15. Pregnant (positive serum pregnancy test), planning to become pregnant during the trial period, breast-feeding, or of childbearing potential and not practicing reliable contraception***.
16. Patient is non-responder to Mitomycin C as a chemical ablation agent for urothelial carcinoma. This criterion relevant only to patient who already participated in another UroGen's studies or any other relevant studies with chemical ablation efficacy endpoint.

§ If both upper tracts meet inclusion criteria, the treating urologist in consultation with the sponsor can decide which side is to be treated within the trial. The other side should be treated as per standard of care, however if the other kidney treatment includes an intravesical instillations, the patient is not eligible. In any case, the other kidney must be free of cancer before the first instillation on the side to be treated in the clinical trial.

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

** Women of non-childbearing potential:

4. At least 12 months since the last menses, or
5. Without uterus and/or both ovaries, or
6. Has been surgically sterile for at least 6 months prior to trial drug administration.

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

11. Investigational product (IP) - MitoGel™ Kit

Detailed information about the investigational product is found in the investigator brochure.

11.1. MitoGel™ Kit Packaging and Labeling

All clinical supplies will be packaged (**Figure 2)**, labeled (**Figure 3-Figure 5**:) and shipped in compliance with cGMP and GDP. All trial provided IP will be appropriately documented (i.e., batch records, Certificate of Analysis, etc.).

11.1.1. MitoGel™ Kit

The **MitoGel™** Kit contains the following components (**Table 1**):

Table 1 MitoGel™ Kit components

Component	Quantity (per Kit)	Function
Mitomycin for Injection, USP (vial) *	2 × 40-mg vials	Active Ingredient
TC-3 Sterile Hydrogel (vial)	1 × 20-mL vial	Sustained release medium
Blank MitoGel™ Admixture Labels	5	Once Admixture ready to be completed and affixed on the: Vial, Protective Bag, pharmacy book, patient study file
Light Protective Bag	1	Protects MitoGel from light
MitoGel™ Admixture Syringe Label	1	To be affixed on the syringe at the treatment area.
Instructions for Pharmacy (IFP)	1	Instructions for MitoGel Admixture Preparation.

* USP = United States Pharmacopeia; The MMC is provided as a dry lyophilized powder.

** The 20 mL of "TC-3 Sterile Hydrogel" is provided in a 25-mL glass vial.

Figure 2: Sample of the Kit Box

Caution: New Drug-Limited by Federal (or United States) Law to Investigational Use

MitoGel™ Kit

UroGen Pharma Ltd., 9 Ha'Ta'asiya St., Ra'anana, Israel. Tel: +972-77-4171412
For instillation to the upper urinary tracts

Each Kit contains

Quantity per Kit	Manufactured by	Component
2 x 40 mg vials	Cenexi for UroGen Pharma Ltd.	Mitomycin for Injection, USP (vial)
1 x 20 mL vial	Isorad for UroGen Pharma Ltd.	TC-3 Sterile Hydrogel (vial)
5	B&C Group for UroGen Pharma Ltd.	Labels
1	B&C Group for UroGen Pharma Ltd.	Preparation Leaflet

Rx only

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).

Once prepared as MitoGel™ Admixture, keep in the vial at room temperature and protected from light.

Use the Instructions for Pharmacist leaflet while preparing the MitoGel™ Admixture.

Packed for: UroGen Pharma Ltd.

Packed by: B&C Group, Watson & Crick Hill, Rue-Granbonpré 11, B-1435 Mont-Saint-Guibert, Belgium. Tel: +32-10-237444

Kit Batch Number: Mfg Date:

Kit serial Number:

* Format presentation. Data will be updated according to batches manufactured.

Figure 3: MitoGel Kit Label Format

Caution: New Drug-Limited by Federal (or United States) Law to Investigational Use

Mitomycin for Injection, USP, 40 mg, for instillation to the upper urinary tracts when used in MitoGel™ Admixture

Rx only

Storage: Retain the vial in the carton. Store dry powder at 25°C (77°F), excursion permitted between 15°C (59°F) and 30°C (86°F), protected from light. Avoid excessive heat (over 40°C, 104°F).

Mfd for: UroGen Pharma Ltd. 9 Ha'Ta'asiya St. Ra'anana, Israel.
Tel: +972-77-4171412

Mfd by: Cenexi-Laboratoires Thissen,
S.A. rue de la Papyrée 2-4-6 B-1420 Braine-l'Alleud, Belgium.
Tel: +32-2-386-1400

Batch Number: Mfg. Date: MMMYYYY

Figure 4: Mitomycin for Injection, USP Label

Caution: New Drug-Limited by Federal (or United States) Law to Investigational Use

TC-3 Sterile Hydrogel for instillation to the upper urinary tracts when used in MitoGel™ Admixture

Volume: 20mL

Storage: Store at 25°C (77°F), excursion permi (86°F). Avoid excessive heat (over 40°C, 104°F).

Ingredients: Poloxamer P407, hydroxypropyl methylcellulose, polyethylene glycol 400, water for injection.

Mfd for: UroGen Pharma Ltd. 9 Ha'Ta'asiya St. Ra'anana, Israel.
Tel: +972-77-4171412

Mfd by: Isorad Ltd., P.O. Box 239, Yavne, 8110102, Israel.
Tel: +972- 8-943-4710

Batch Number: Mfg. Date: MMMYYYY

Figure 5: TC-3 Sterile Hydrogel Label

The components of the MitoGel™ Kit are produced under aseptic conditions and according to current Good Manufacturing Practice (GMP) (European Commission, May 2003 Guidelines) and FDA "Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice", September 2004.

The MitoGel™ Kit lots used in this trial are tested and their release is supervised and

approved by the UroGen QA Department.

11.2. Investigational Product Acquisition, Dispatch, and Storage

11.2.1. Initial Supply

Initial clinical supply shipment will be sent automatically to sites in which the study was approved by their CA/IRB/EC, when the first patient at the site has been enrolled.

11.2.2. Shipment of Clinical Supplies

The Sponsor/designee will notify the Principal Investigator prior to shipment of drug supplies and other related clinical supplies regarding the anticipated date of their arrival at the pharmacy. Shipment will be sent directly to the delegated personnel at the pharmacy.

All shipped clinical supplies will be appropriately documented to ensure proper handling in case of emergency.

Shipment will be sent under controlled conditions. Transportation temperature will be monitored and recorded by temperature-monitoring devices loggers.

Each shipment of clinical supplies for the trial will contain a certificate of analysis and a shipment certificate detailing the content of shipment.

The pharmacist or study coordinator (in case of ancillary clinical supplies required for MitoGel instillation procedure) who receive the shipment will review the shipment items against the shipping certificate supplied to assure adequacy of shipment. In addition, the temperature logger will be read and the output will be printed for the pharmacy's records, assuring the shipment has arrived in good condition according to requirements. If all is OK, he/she will confirm receipt in the eCRF system

11.2.3. MitoGel™ Kit Storage and Handling

The MitoGel™ Kit must be stored under controlled conditions and in accordance with applicable regulatory requirement(s) for cytotoxic substances.

Retain the vials in the carton until use. Store the kit at 15-25°C (59-77°F). Avoid excessive heat (over 40°C, or 104°F). Once prepared as MitoGel™ Admixture, keep in the vial at room temperature and protect from light.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the above instructions. Documentation of temperature monitoring should be maintained at all times until study closure.

11.2.4. MitoGel™ Admixture Stability and Handling

Store the vial at 15-25^{0}C (59-77^{0}F). One hour before administration place in refrigerator, or in any other cooling apparatus at 2-8^{0}C (35-46^{0}F) to liquefy the MitoGel™ Admixture for the instillation. Keep protected from light. Avoid exposure to excessive heat (over 40°C, or 104°F)

The MitoGel should be instilled up to 9hrs from end of preparation.

11.2.5. Clinical Supplies Quality Complaint Handling Procedure

A product quality complaint (PQC) is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, i.e., any dissatisfaction related to the identity, quality, quantity, durability, or reliability of a product, including but not limited to its labeling or packaging integrity.

The impacted MitoGel™ Kit or ancillary supplies must be marked “not for use” and quarantined during investigation and until a decision has been made by the sponsor regarding the drug’s validity. In case of MitoGel, the quarantined kits should be kept at the required temperature to allow future use if approval is received by quality assurance personnel of the sponsor. Reporting must be done upon first awareness, and the site should await the sponsor's written decision regarding the drug's validity prior to drug dispensing.

PQC forms will be supplied to the site and pharmacy at trial start. In case of any temperature deviation, either during transport or storage at the pharmacy, or any problem (as specified above) with supplied clinical ancillary supplies (injector, catheters etc.), it is the site investigator's responsibility to assure the completed PQC is sent to the sponsor via email/fax immediately, to allow proper monitoring of complaints relating first, to patients safety, monitoring of site's supplies inventory.

Any PQC written report must be reported immediately to the site CRA & Sponsor by email:

ATTN: Quality Assurance

qa@urogen.com

Following review of the quality complaint form, the sponsor will send written approval to allow the use of the affected Kit/s, or request for kit destruction. In case a kit should be destroyed, it will be disabled in the system by the site pharmacist or sponsor, and will not be available for dispensing.

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.

11.3. MitoGel™ Admixture Dosage, Preparation, Dispensing and Administration

11.3.1. Dosage Determination

MitoGel ™ Admixture dose will depend on the patient's pelvicalyceal volume.

MitoGel ™ Admixture concentration will be 4mg/mL (4mg MMC in 1 mL of TC-3).

Enrolled patients will receive 6 weekly instillations given in a retrograde fashion.

CR patients will undergo additional, monthly maintenance instillations of the same concentration, up to 12 months following PDE visit.

The volume of the MitoGel™ Admixture to be administered and thus, the final dose, will be individualized and will be based on volumetric measurements of the pyelocalyceal system using pyelography. For better accuracy, the volumetric measurement should be repeated 3 times. The volume of MitoGel™ Admixture instilled will be 100% of the measured pyelocalyceal system volume: average of the three measurements. The average of the three measurements is the instillation volume. In case the number contains decimal fraction, please round it as follows:

≥0.5 - round it up to the closest whole number.

<0.5 - round it down to the closest whole number.

The administered volume should be identical to the mean measured volume and will not exceed 15 mL (a maximum total dose of 60 mg MMC), whichever is lower (For detailed instillation instructions please refer to the IFU).

The volumetric measurements should be documented in the source data and the CRF

11.3.2. MitoGel™ Kit Dispensing

The investigator or coordinator will be responsible for notifying the responsible person in the pharmacy ahead of time of the participants scheduled instillation visit.

Prior to every treatment, investigator/coordinator will dispense MitoGel Kit in the EDC system (Target), obtaining the number of MitoGel kit to be withdrawn from the pharmacy stock.

Withdraw of MitoGel ™ Kit from inventory for the preparation of the MitoGel ™ Admixture will be done only after the investigator has provided designated prescription with patient details according to the trial specific supplied prescription, and supplied MitoGel kit number.

In clinical sites using their own systems for ordering MitoGel Admixture (instead of UroGen supplied prescriptions for the trial) the drug order wording MUST be:

"Please dispense 1 vial of 4mg/ml MitoGel Admixture, according to the IFP" OR

"Please dispense at least 17ml of 4mg/ml MitoGel Admixture, according to the IFP" OR

In sites where the inclusion of exact volume is mandatory in the drug order the wording will be: "Please dispense 17ml of 4mg/ml MitoGel Admixture".

The maximal volume to be administered to a patient is 15ml. The drug order should NOT request 15ml of MitoGel since the adjustment for the individualized volume will be done by the clinical team at the treatment center.

The MitoGel™ Admixture will be dispensed only to authorized site trial personnel. Dispensing must be documented in the study accountability log.

In case the instillation has been cancelled the pharmacist must document in the study accountability log that the Admixture was prepared but not dispensed to the patient.

In case the instillation was cancelled after MitoGel™ Admixture was dispensed, it is the investigator responsibility to notify the pharmacy about the cancellation.

Returned MitoGel™ Admixture must not be dispensed again, even to the same patient, and must be destroyed. MitoGel™ Admixture may not be relabeled or reassigned for use to other patients.

In case MitoGel kit was dispensed in the EDC system but eventually was not opened/not used, and kit was kept at required storage conditions at the pharmacy, the MitoGel kit may be returned to the site stock but ONLY after coordination with Sponsor/Designee.

11.3.3. Preparation

MitoGel™ Admixture will be prepared according to the Instructions For Pharmacy (IFP) document provided in the MitoGel™ Kit.

When not using the trial-supplied labels, the MitoGel™ Admixture Vial label should contain at the minimum the following information:

- <Trial Identifier, preferably TC-UT-03-P>
- <Subject Identifier, preferably subject enrollment ID>
- "MitoGel™ Admixture 4mg/ml (Mitomycin C 4mg per 1mL)
- Kit Batch Number _____
- "For instillation to the upper urinary tract"
- "Note: Maximum patient dose is 15mL (60mg)
- "Storage: Store up to 8 hours at room temperature protected from light"
- "Caution: New Drug-Limited by Federal (or United States) Law to Investigational Use"
- Prep. Date:
- Exp. Date and Time:

MitoGel™ Admixture Syringe label

Admixture label for the syringe is provided within the MitoGel kit. It must be used. The pharmacists can either complete or not complete it, but it must be sent to the site along with the Admixture vial. If not completed by the pharmacist, the syringe admixture label should be completed by the person withdrawing admixture from the vial into the syringe and affixed onto the syringe, prior to treatment.

11.3.4. IP Administration

MitoGel™ Admixture will be administered by study authorized person as documented in the delegation log and only after proper training was given regarding the instillation procedure.

The pharmacy will dispense a 17-20 mL MitoGel™ Admixture for every instillation regardless of the individual volume required. Prior to every instillation, the treating investigator/designee must review the pyelocalyceal volume measurement recorded in the patient file and complete the designated MitoGel administration form which is provided by UroGen, with the required volume for instillation. The volume will be verified by site team observer. Both treating investigator/designee and observer will sign the administration form, thus confirming the correct volume will be instilled.

Thereafter the treating investigator/designee will withdraw the exact volume required into the syringe.

Once instillation is over, the treating investigator or designee who performed the instillation must complete the actual volume instilled and sign the administration form. The administration form must be filed in the study patient file. These steps MUST be repeated at each instillation.

The Admixture will be instilled in a retrograde fashion via ureter catheter. In exceptional cases after approval by the trial coordinating PI, instillation through a nephrostomy tube may be conducted.

Due to the viscose nature of the Admixture the instillation must be done using the designated Injector Device supplied by UroGen. For detailed instillation instructions please refer to the Instructions for Use (IFU) document as well as UroGen's Injector Device Instructions for Use Manuel.

11.3.5. IP Instillation Schedule

MitoGel™ Admixture will be administered for therapy in the pyelocalyceal system as 6 once-a-week, consecutive instillations, at Weeks 1, 2, 3, 4, 5, and 6. Drug administration will be documented in the patient file, Case Report Forms (CRFs), and in the Drug Administration Records. For CR patients, additional instillations will be administered until 11M FU visit or until tumors' recurrence.

11.4. IP Accountability

The investigator is responsible for ensuring that all MitoGel™ Kits received at the site are inventoried and accounted for throughout the trial. The MitoGel™ Kit should be dispensed under the supervision of the investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. The dispensing of a MitoGel™ Admixture to a patient will be documented in the pharmacy drug accountability form or electronic drug accountability logs.

The MitoGel™ Kit must be handled in strict accordance with the protocol and the container label, and must be stored at the site's secure drug room or Pharmacy at a limited-access area under appropriate storage conditions.

Unused MitoGel™ Kits must be available for verification by the sponsor's site monitor during on-site monitoring visits. The return to the sponsor of unused or expired MitoGel™ Kits will be documented on the drug return form. Destruction of unused MitoGel Kits may be done on-site following written approval by the sponsor. Destruction must be documented in the "IP destruction form".

Used (Empty) MitoGel ™ vial or kit boxes should be discarded after use and will not be reviewed by the sponsor's site monitor.

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

11.5. Replacement of Unusable MitoGel™ Kits

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

In addition, unusable kits will be disabled in the EDC. Disabling of the kit will trigger shipment of replacement kit, in case kits are scarce at site.

Site should also notify of the need for additional MitoGel kits to the site CRA and email the sponsor's operations: logistics@urogen.com.

11.6. Assessment of IP compliance

At each treatment visit the actual dose administered will be documented in the Administration Form, which will be filed at the study file, and data recorded in the CRF, thus allowing monitoring of IP compliance.

11.6.1. Assessment of the other treatment related drugs compliance

At each treatment visit, the site team will check the compliance of the patients taking the bicarbonate and antibiotics and results will be recorded in the patient’s file and in the CRF. The sites are requested to document the bicarbonate compliance on the supplied compliance log.

Anti-histaminic drugs and relaxants are prescribed at the investigator's discretion therefore the data will be reviewed but not assessed for compliance.

11.7. Destruction of IP

Used MitoGel™ Kit vials should be discarded locally according to local institution guidelines for cytotoxic waste destruction.

Unused MitoGel™ Kits must be available for verification by the sponsor’s site monitor during on-site monitoring visits and will not be destroyed prior to Sponsor approval. Once destruction is approved, site will destroy the kit locally and will document it in the destruction form and accountability log.

MitoGel™ Admixture vial and used syringe will be discarded at the clinic/urology department according to local institution guidelines for cytotoxic waste destruction

12. Safety Evaluation

12.1. Safety Assessment Prior and During the Treatment Period:

12.1.1. Adverse Event Collection

- The patient's condition will be monitored throughout the study. At each visit, adverse events (AEs) will be elicited using a standard non-leading question, such as “How have you felt since the last visit?” In addition, any AE signs or symptoms that are observed will be documented;
- The AE/safety assessment will be conducted by the investigator or qualified clinical staff. The Investigator or qualified clinical staff will record the AEs on the Adverse Event Log provided in each patient’s chart and CRF;
- The study period for AEs collection is defined from the ICF signature and up to 30 days following the last administration of investigational product unless the AE is suspected to be related to the study treatment, in such case the AE should be reported regardless to the timelines of the reporting period (refer to section 19.2);
- All AEs will be collected as follows:
  - The patients’ response to questions about their health,
  - Symptoms spontaneously reported by the patient to be recorded in the CRF,
  - Clinically relevant changes and abnormalities observed by the Investigator (e.g., local and systemic tolerability, clinically significant laboratory measurements confirmed by repeated measurement, vital signs, results of physical examinations);
- If an AE worsens in intensity, it should be recorded as a new AE. If an AE gets milder in intensity, it continues as the first report until the patient is recovered.

12.1.2. Action Taken and Follow-up of AEs

AEs requiring intervention must be treated according to the standard care procedures to protect the health and well-being of the patient. Appropriate resuscitation equipment and medicines must be available to ensure the treatment of an emergency situation.

Treatment due to an AE will be recorded as concomitant medication.

12.1.3. Follow-up of AEs

The investigator will follow up on each AE until it is resolved, until the medical condition of the patient is stable, or until the AE is otherwise explained by the PI. All relevant follow-up information will be reported to the sponsor. The outcome of an AE will be classified as

recovered, recovered with sequelae, not yet recovered, or death.

Adverse events will be reported according to Section 19- "Management of Adverse events".

12.2. Telephone Contact 24–32 Hours Post-treatment

For patients treated via retrograde fashion only:

After each instillation in the treatment period, the patient will be given a questionnaire with the questions, and will be notified that the site will contact him/her the day after to collect the answers. Questions are:

- How long after the treatment did you have your first urination?
- How long after the treatment was the urine clear (no purple color) for the first time?

Twenty-four (24) to 32 hours post each instillation, the patient will be contacted (via telephone) and information for the questionnaire will be collected answers will be completed and form will be signed by the site. At this point, any spontaneously reported adverse events will also be recorded. If necessary, a patient may be summoned for an unscheduled visit to follow up on any post treatment adverse event that requires clinical evaluation or follow-up. See Appendix IV.

12.3. VAS Questionnaire - Pain Assessment During Treatment

Following each of the instillations 1-6 the patients will be requested to mark the degree of pain they felt during the IP instillation (and not during catheter insertion), in a VAS questionnaire 0-10 (100mm scale). The study coordinator than will measure with cm ruler from left to right and document the degree of pain in the patients' file and CRF [Wewers ME, Lowe NK, 1990].

12.4. Tests for Assessment of Safety

12.4.1. Pregnancy Test

A pregnancy urine test will be conducted in female participants of childbearing potential in each of the study visit. If positive, a pregnancy blood test will be performed to verify. A female is considered of childbearing potential unless she is:

- At least 12 months since the last menstrual bleeding; or
- Without a uterus and/or both ovaries; or
- Has been surgically sterile for at least 6 months prior to trial drug administration.

12.4.2. Clinical Evaluation

At the specified visits, a full physical exam or urology-oriented physical exam 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. Vital signs (including heart rate and blood pressure, temperature, and respiration rate) will be taken See **Appendix I** & **Appendix II**.

12.4.3. Laboratory Assessments

All general blood and urine specimens will be analyzed by Local lab (**Appendix III** for the listing of tests). Blood samples for analysis of plasma level of Mitomycin (Pharmacokinetics) will be sent to the central PK lab (Appendix VII: Collection and Handling of Plasma Samples for MMC Pharmacokinetics).

13. Trial Conduct and Procedures

Pre-Screening stage- this stage in aiming to eliminate the screening of patients without the potential to meet the study criteria due to some complexity of their situation which can affect their compliance, and also to improve the adherence to the protocol procedures and timelines. This stage is very important due to the complexity of this protocol. The sites will be given a pre-screening questionnaire which they should fill-in in a timely manner and send it to the sponsor prior the consenting process.

13.1. Patient Eligibility Review and Enrolment to the Trial

- Every patient must first sign the informed consent.
- In order to obtain screening number, the site will need to register the patient in the electronic CRF (eCRF).
- Soon after patient registration, the site will email to the site CRA and UroGen personnel Dr. Ifat Klein and Tami Gerassi the de-identified source documents accompanied by completed submission form, **no later than 7 working days after the screening visit**. In addition, site will upload the Pyelography/CT/MRI images relevant for taking the eligibility decision to the secure AG MedNet. The documents and images must be patient de-identified (with no personal patient identifiers) prior to upload.
- Prior to the first instillation on Visit 1 (V1), patient eligibility to the trial must be confirmed by the sponsor. The sponsor will consult with the trial principle coordinating

investigator (Dr. Seth Lerner) on a case by case basis and will notify the site investigator via email about the patient's eligibility.

- Upon eligibility approval, the site will record the approval in the eCRF and will perform patient enrollment. Patient enrollment number will be given automatically by the CRF. **Enrollment of patient into the trial must occur prior to the day of first instillation to allow enough time for kit dispensing via the EDC and preparation of the IP.** Refer to section 23.2 for patient registration, and enrolment procedures.

13.2. Screening Visit (V0): -4 to -1 weeks

Following the informed consent process and mutual signatures on the ICF, potential patients will undergo the following screening procedures:

- **Review of eligibility criteria** and determination of the patient's eligibility based on patient file and medical history;
- **Medical history** - Including specific information regarding previous recurrences of urothelial carcinoma in the bladder, urethra, ureter and in the UUT; including information about the Tumor stage, grade, morphology etc. (according to the documentation level in the CRF.);
- The following documentation is required only for enrolled patients. **Default Planned UTUC Treatment Documentation** had the patient not been enrolled in the trail;
- **Smoking history** documentation (current smoker? Number of years, cigarettes per day, smoking stop date);
- **CTU** - In the event that a CTU from the last 3 months is not available, or the one that is available does not reflect the current disease episode, or in the event that the investigator believes that an updated CTU in the screening will lead to a better tumor evaluation due to a patient's specific anatomy a new one should be obtained during the screening period; in the event that CTU is not applicable for any reason, an MRI should be performed instead.
- **Concomitant medication** – All ongoing medications/therapies, including prior therapies & procedures given for the previous urothelial carcinomas;
- **General physical exam**, urology oriented physical exam, vital signs measurements (**Appendix I & Appendix II**);
- **Blood tests** (**Appendix III**);
- Urinalysis and Urine Culture to rule out UTI

- **Pregnancy serum test** (for women with childbearing potential **Appendix III**);
- **Upper tract wash urine cytology** - The upper tract wash urine cytology can be collected using ureteroscope or ureteral catheter (wash), **before** any biopsy or topical treatment was done.
- **Biopsy for histopathology** - should be performed prior to recording tumor size and location.

  UUT urine cytology and biopsy need not be repeated if done within the past 2 months (or 3 months prior to the first instillation), provided the records can be made available for the trial and the slides can be reviewed by the trial central pathology service. In this case, patients should be scheduled for a Screening Visit, during which URS for lesions mapping (when it was not documented properly within 8 weeks to the screening), and documentation as well as pyelography and volumetric estimation will be performed as described above (if not done as part of the SOC before the screening).

  In the event that a patient has undergone surgical procedure in which the lesions were partially removed (i.e. de-bulking), the surgical procedure should be documented in the patient's medical history record;

- Diagnostic URS with C-ARM pyelography in order to demonstrate the pyelocalyceal system, by two views: 1. Superior view; 2. Oblique view in order to reveal hidden calyx / baseline UUT lesion assessment and videotape/photography record (if not done within past 2 months or if the documentation wasn't done according to the protocol requirements):
  - Number, location (upper calyx, middle calyx, lower calyx, renal pelvis, UPJ), size by visual estimation (the longest diameter); the measurement shall be performed post biopsy.
  - Lesion appearance (visually described as papillary, solid, nodular, or sessile). Information must be recorded in the worksheet "UUT Lesion Documentation Form" provided by the Sponsor.
  - In case URS needs to be repeated at screening but the investigator does not wish to repeat the test due to medical considerations (e.g., general anesthesia), a CTU can be performed instead if this test can reflect the tumors status for the specific patient (e.g., tumors is bigger than 4mm)

- Pyelography for assessment of the upper tract anatomy and volume measurement: The volumetric measurements of the "Pyelocalyceal System" (PS) should be performed under fluoroscopy and be documented. The "Contrast Agent admixture 20%" (CA) shall be injected to the PS, until the CA start to flow backwards below the UPJ. The estimated total volume to be injected may vary due to patient's PS anatomy. The volumetric measurements shall be repeated three times followed by mean calculation of the CA injected to the PS. MitoGel™ volume to be instilled to the PS shall be 100% of the measured PS or 15mL, whichever is lower. The volumetric measurement should be documented in the source data and the CRF;
- If a single J in-dwelling ureteral catheter is to be used for instillation, catheterization can be done at any time during the screening period prior to treatment. In case that single J catheter remained in the pyelocalyceal system, reduce from the measurable volume 1 mL IP (dead volume) which is left in the catheter (e.g., measured volume is 11 mL the volume to be injected is 10mL). Following the instillation, the single J catheter should be flushed with 1.5mL of WFI in order to keep the catheter shaft open.

The decision on whether to enroll patient into the trial will be based on the histopathology and cytopathology results obtained from the local institutional pathologist; however, all biopsies and urine cytology obtained at Screening/baseline (or earlier if within 2 months of screening) and at PDE will be reviewed again centrally. The results of the central reading will be used as a sensitivity analysis.

The sponsor highly recommends to wait for the central review prior the beginning of any treatment administration to have a better confidence that the patient is having LG disease.

- Once all eligibility criteria have been confirmed, the patient will be registered into the trial by receiving an enrollment number. This should take place prior to treatment with sufficient lead-time to allow for preparation of the IP by the pharmacy;
- Patient should be prescribed with sodium bicarbonate in advance and should be given written instructions to consume 1.3 g of Sodium Bicarbonate the night before instillation, the morning of, and 30 min (total of 3.9 g) prior to the instillation, in case that patient is planned to be anesthetized, bicarbonate may not be taken 30 minutes prior to the treatment. If patient is enrolled, a reminder phone contact to the patient should be done the day before the instillation;

- Aiming to minimize the risk for Urinary Tract Infections (UTI), especially Acute Pyelonephritis, anti-microbial prophylaxis (e.g., Ciprofloxacin) should be prescribed according to the AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (See Appendix VI: Recommended Antimicrobial Prophylaxis for Urologic Procedure);
- Prophylactic anti-allergic treatment – Anti-histaminic agents to be taken the day before instillation, on the day of instillation and up to three days after the instillation; this treatment will be at the investigator's discretion.
- It is recommended to allow the patients using a relaxing pill such a diazepam 5-10 mg (or any other relaxation pill) to reduce the anxiety before each of the instillations;
- Patient should be given patient guidance letter for UUT MMC-TC-3 Gel instillation.
- Patient should be provided with a patient card with treatment information and investigator details to be contacted in case of an emergency;
- Patient should be provided with a letter notifying his general physician about his participation in the study.

13.3. Treatment Visits

The pharmacy should be notified ahead of time regarding the required preparation of MitoGel™. Prescription signed by the investigator must be provided ahead.

13.3.1. General Instructions for Instillation Visits

- **In the first part of the study, all enrolled patients will undergo six (6) weekly UUT instillations** - (± 3 day).
- **Prior to MitoGel™** administration, except the first treatment, the treating investigator MUST review the last patient's safety lab results to determine if the instillation can be performed as planned. The review must be documented in the patient medical file prior to study treatment.
- Following are the threshold parameters for acceptable laboratory values prior to each treatment*, blood tests will be performed according to Appendix III. These tests must be done no longer than 3 days prior to the instillation and can be done also in the patient's local clinic** if not feasible to have them done within short time period in the hospital:
  - 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/1.73m2, 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/1.73m².

* The results of these specific test must be reviewed prior to each treatment.
Exception in Visit 1: Tests should be taken but results may be reviewed after the treatment.

If laboratory parameters do not conform to the detailed above, treatment will be postponed until laboratory values improve, for up to 4 weeks.

- **In the event of urinary tract infection or another safety reason which causes the PI to postpone a treatment, the treatment will be postponed until the event is resolved and not over 4 weeks; In case treatment has been delayed beyond 4w due to ADR (adverse drug reaction) study treatment will be discontinued permanently however study follow-up will be continued.**
- **Volume of MitoGel™ Admixture to be instilled** (see Screening [V0] for details) –
  - The volume to be instilled will be based on estimation of the pyelocalyceal space conducted during the screening / prior to treatment initiation.
  - The volume of contrast agent required to fill the pyelocalyceal space (without causing distention) shall be measured.
  - To increase accuracy, an average of three (3) measurements should be carried out. In case the number contains decimal fraction, please round it as follows:
    ≥0.5 - round it up to the closest whole number.
    <0.5 - round it down to the closest whole number.
  - Repeated volumetric measurements may be performed prior to each instillation, at the discretion of the treating investigator.
  - The volume of MitoGel™ instilled will be 100% of the estimated pyelocalyceal volume or 15 mL (whichever is lower); all the measurement procedure and each of the three (3) measurement must be recorded in the patient's source document and in the CRF.

- **Sodium Bicarbonate:** The Patient will be given 1.3 g Sodium bicarbonate tablets AND written instructions/dosing diary to consume 1.3 g of Sodium Bicarbonate orally, the night before the instillation, the morning of instillation, and 30 minutes prior to the instillation procedure (total of 3.9 g); in case that patient is planned to be anesthetized, bicarbonate might not be taken 30 minutes prior to the treatment.
- **Diuretics**: It is preferred that diuretics not be taken the night before and prior to the instillation. If a patient is on diuretic medications, the PI should determine, based on his/her clinical judgment whether the medication can be skipped prior to the instillations as recommended above and should advise the patient on the diuretics use during the study;
- **Pre-instillation drinking:** General guidelines for drinking instruction pre- and post-instillation are included below. The need for de-hydration will be decided by the physician based upon the clinical guidelines mentioned herein:
  - To the extent that it is possible, drinking should be avoided in the 4-6 hours prior to the instillation.
- **Post instillation drinking should be limited**. A recommended drinking schedule follows:
  - 0-2 hours post instillation: refrain from drinking any liquid;
  - 2-4 hours post instillation: 1 cup of water every 2 hours;
  - 4 hours post instillation: resume normal liquids consumption ;
  - Following instillation, the patient will be carefully monitored for urine output and clinical symptoms, which might indicate urinary obstruction. Special caution should be taken in single kidney patients. Pre and post-Instillation Patient's Instructions will be provided to the patient prior to the first instillation (Patient Guidance Letter).
- **Prophylactic antibiotics**: Aiming to minimize the risk for Urinary Tract Infections (UTI), especially Acute Pyelonephritis, anti-microbial prophylaxis will be prescribed (e.g., Ciprofloxacin) according to the AUA Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis (See Appendix VI);
- **Prophylactic anti-allergic treatment –** Prophylactic anti-allergic treatment will be given per PI discretion. Recommended regimen–Anti-histaminic agents to be taken the day before instillation, on the day of instillation and 1-3 days post instillation.
- Diazepam (5-10 mg) (or any other relaxation pill) will be given before instillations according to the PI discretion to reduce the anxiety.

- **Local ointment for protection of skin -** Use of local ointment prior to instillation for reduction of local irritation around the genitalia;
- **Special precautions should be taken with females; the woman shall be instructed to carefully wash the genitalia following each urination during the day of instillation followed by using local ointment on the genitalia.**

13.3.2. Treatments as Needed

- **Management of dysuria -** Local and systemic analgesics administration;
- **Management of other lower urinary tract symptoms (LUTS) such as Frequency/ urgency/incontinence -** Use of anticholinergic agents if not contraindicated;
- **Diazepam 5-10 mg (or any other relaxation pill)** as an optional therapy, to reduce anxiety before each instillation. To be given an hour before. The patient should be cautioned of driving on that day.

13.3.3. Instillation Procedure

- For the instillation procedure the site should first verify they have Protocol TC-UT-03-P ancillaries, Injector device, and IFU manual.
- MitoGel™ Admixture must be instilled by study authorized person as documented in the delegation log and only after proper training was given regarding the instillation procedure.
- For instillation, a 7–8 Fr ureter catheter supplied by UroGen shall be used. In situations where it is technically challenging to pass the 7Fr catheter, a 5Fr Ureteral Catheter with molded Luer-Lock port may be used.
- Due to the viscose nature of the MitoGel™ Admixture the instillation must be done using the designated Injector device supplied by UroGen. Please refer to the UroGen's Injector Device Instructions for Use Manuel for detailed instillation instructions.
- Instillation volume of MitoGel™ Admixture/Administration Form: The pharmacy will dispense a 17-20 mL MitoGel™ Admixture for every instillation regardless of the individual volume required.

Prior to every instillation, the investigator must review the pyelocalyceal volume measurement done for that patient. A repeated volumetric measurements may be performed prior to each instillation, at the discretion of the treating investigator. The investigator must withdraw the exact volume required into the syringe, and document the required volume in the supplied Administration Form. The required

volume information and syringe filling should be completed in the Administration Form, and confirmed by additional trial authorized personnel who should be present at that time. Both must sign the Administration Form before instillation begins. Once instillation is over, the investigator or designee who performed the instillation must complete the actual volume instilled and sign the Administration Form. The Administration Form must be filed in the study patient file.

- To obtain better dispersing of MitoGel™ Admixture in the pyelocalyceal system, the patient should be in Trendelenburg Position (if possible) lying down on the side that should be treated.

  In cases where Trendelenburg Position can't be obtained, the patient should lie down (if possible) on the side that should be treated.

The following procedures should be conducted during all instillations:

- Prior to MitoGel™ administration, cystoscopy should be performed (SOC) to obtain screening of the urethra and the bladder for abnormal findings.
- **Pyelography**- Prior to every instillation pyelography with contrast agent shall be performed to demonstrate pyelocalyceal system for abnormal findings and to verify that the catheter tip, is located above the UPJ for proper instillation to the renal pelvis. The technique for an office-based approach for placement of ureteral catheter has been previously described (Nepple, 2009). If a single J catheter is being used, the insertion of the catheter can be done prior to the treatment visit under pyelography (see above).
- Placement of guidewire and ureteral catheter shall be performed under fluoroscopy.
- Advance guidewire through the cystoscope working channel via the ureter to the renal pelvis.
- Anchor the guidewire in the renal pelvis and remove the cystoscope.
- Advance the ureteral catheter over the guidewire to the preferable location in the renal pelvis and take photos to document the location of the catheter tip. Preferable location will be considered as the place where the flow from the catheter tip of the investigational product will enable best coverage of the renal pelvis and the calyces.
- MitoGel™ Admixture administration shall be according to individual dose/volume (Installation instructions-to be provided in the study manual);
- The same documentation is required also for patients administered through a nephrostomy tube:

In case of instillation via nephrostomy tube – the nephrostomy tube types allowed are Silicon or Simplastic.

Latex is not allowed, due to fear of rupture.

At the end of the instillation the catheter must be washed with 2 cc of saline, to remove remaining MitoGel™ Admixture. Prior to patient leaving the clinic the site staff must verify that the patient urinates via the nephrostomy tube, by watching the urinary bag filling.

13.3.4. Instillation #1 Visit Procedures (V1):

The following procedures should be conducted prior to 1st instillation:

- It is recommended to perform the first instillation in the OR under sedation.
- Patient reminder phone call shall be done a day before the treatment regarding antibiotic treatment, bicarbonate, antihistamine (if applicable) and limited drinking and diuretics;
- Confirmation of patient's eligibility;
- Confirmation that the safety labs results are available.
- Confirmation of limited drinking and/diuretics as per need;
- Safety assessment, see Section 13.3.6;
- On treatment day - Verification of consumption of oral dose of 1.3 g of sodium bicarbonate the night before the instillation, at the morning of and 30 minutes prior to the instillation procedure; Completion of bicarbonate compliance log. In case that patient is planned to be anesthetized, bicarbonate should not be taken 30 minutes prior to the treatment.
- Verification /administration of prophylactic anti-biotic treatment
- Verification of consumption of oral dose of prophylactic anti-allergic treatment (if applicable). The anti-histaminic agents should be consumed the day before instillation, on the day of instillation and 1 to 3 days following the instillation.
- Pre-Dose MMC PK blood draw (when applicable; See PK instructions, Appendix VII: Collection and Handling of Plasma Samples for MMC Pharmacokinetics);
- Evaluation and recording of AE and concomitant medications;
- Urology oriented physical exam & vital signs measurements (**Appendix II & Appendix III**);

- Blood tests (**Appendix III**); In case patient preformed all required blood test according to **Appendix III** up to 3 days prior to the instillation- no need to repeat;
- Urinalysis/dipstick;
- Review of urine culture results from the Screening Visit;
- If urine dip-stick is positive for pregnancy, serum pregnancy test should be performed. In this case, the instillation should be postponed until the serum pregnancy test results are available. If pregnancy test is positive, patient should be discontinued from study.

The following procedures should be conducted post instillation:

- Recording of pain during the instillation procedure by the patient, by marking the score on the 0-10 scale VAS for pain*.
- Following the **first** instillation, the patient should remain in the clinic/hospital for at least 6 hours for general observation; the patient will not be discharged before the first free urination. The medical team should document the patient assessment timely before leaving the clinic.
- At the first treatment subset of patients (N=6) who gave informed consent, PK samples will be collected for MMC plasma level measurements; a notification will be sent to the study sites, when all the six specimens will be completed in order to stop offering the other patients this procedure. If from some reason, a sample from a patient will be destroyed, another patient will be picked to complete the quorum.
  - MMC plasma level measurements:

    The samples will be collected at 0 (pre-dose) and 30 min, 1, 2, 3, 4, 5, and 6 hours post instillation. At each time point, 3 mL of blood will be collected to yield at least 1.5–2 mL of plasm after centrifugation. Altogether, a total of approximately 24 mL of blood will be collected for PK samples for each patient who signed an informed consent and contributed to this portion of the trial. The plasma samples will be analyzed by validated bioanalytical assay.

    For detailed information, please refer to Appendix VII: Collection and Handling of Plasma Samples for MMC Pharmacokinetics;

- Recording of AE post instillation;

* Local pain will be assessed by the Patient using a Visual Analogue Scale (VAS) provided by UroGen.

- Documentation of concomitant medications;
- Telephone contact 24–32 hours post treatment (section 13.3.7);
- Patient should be given or prescribed (not recommended) with 1.3 g Sodium bicarbonate tablets AND written instructions to consume 1.3 g of Sodium Bicarbonate the night before instillation, the morning of, and 30 min (total of 3.9 g) prior to the instillation;
- 24-30 hour questionnaire should be provided;
- A reminder phone call to the patient should be done the day before treatment.

13.3.5. Instillations #2–#6 Visit Procedures (V2–V6):

- The allowed visit window deviation is ±3 days.
- **A reminder phone call** to the patient should be done the day before the treatment regarding the following:
  - Confirmation that the safety labs results are available.
  - Bicarbonate and antibiotic, antihistamine (if applicable) and limited drinking /diuretics uptake;

The following procedures should be conducted prior to every instillation:

- Verification of consumption of oral dose of 1.3 g of sodium bicarbonate the night before the instillation, at the morning of and 30 minutes prior to the instillation procedure; In case that patient is planned to be anesthetized, bicarbonate should not be taken 30 minutes prior to the treatment.
- Verification of consumption of oral dose of prophylactic anti-allergic treatment. Where used, the anti-histaminic agents should be consumed the day before instillation, on the day of instillation and the day after the instillation.
- Confirmation of limited drinking and/diuretics as per need,
- Safety assessment, see Section 13.3.6;
- Evaluation and recording of AEs and concomitant medications;
- Urology oriented physical exam & vital signs measurements;
- Blood tests according to **Appendix III**; in case patient preformed all required blood test according to **Appendix III** up to 3 days prior to the instillation - no need to repeat;
- Urinalysis/dipstick;
- Urine Culture (only when applicable);

- Urine test for pregnancy - when applicable;
- Serum pregnancy tests may be performed only if urine test is positive for pregnancy-results must be available before the next instillation. In the case that a serum pregnancy test is conducted, the instillation should be postponed until the serum pregnancy test results are available. If pregnancy test is positive, patient should be removed from study.

The following procedures should be conducted during the instillation:

- Prior to IP administration, cystoscopy should be performed (SOC) to obtain screening of the urethra and the bladder for abnormal findings.
- Cystoscopy for catheterization as described herein above followed by ureteral catheter placement under fluoroscopy in the preferable location in the renal pelvis;
- MitoGel™ Admixture administration according to individual dose/volume;
- Patients will be requested to record VAS for pain to describe the degree of pain they felt during the instillation procedure. The patients will complete the VAS immediately after the procedure (only at visits 1-6).

The following procedures should be conducted post instillation:

- Recording of AE post instillation;
- 24-32 hour questionnaire should be provided (only at visits 1-6);
- Telephone contact 24–32 hours post treatment (section 13.3.7) (only at visits 1-6);
- CBC (complete blood count), renal and liver function tests - Should be performed in 1st week and 3rd week following the 6th instillation. This blood test can be performed also in the patient's local clinic. Results should be recorded in the CRF.

13.3.6. Safety Assessment Prior and During the Treatment Period

In addition to general inquiry about patient's condition, prior to each instillation, the physician should query the patient specifically regarding pain, especially in the lower abdomen, flank, or urethra. The physician should also inquire whether the patient has experienced symptoms suggestive of obstruction, urinary tract infection, or allergic reaction to MMC. If symptoms of obstruction/UTI or allergy are backed up by physical/laboratory tests treatment will be postponed until symptom resolution.

In cases of allergic response to MMC, antihistamines with/without cortisone treatment may be administered at the physician's discretion. Allergic response severity must be assessed according to CTCAE version 4.03 in Appendix VIII.

Any unexpected AE related to MitoGel™ and qualified per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) as grade 3 or 4 will be evaluated by the sponsor medical team and steering committee. In case of need, a DMC meeting will be gathered.

The following information about the AE must be included in the CRF:

- Reporting person details;
- Adverse event and relevant clinical findings;
- Time/date of onset;
- Time/date of recovery;
- Intensity/Severity (mild, moderate, severe, life threatening, lethal);
- Action taken on study drug;
- Other actions taken to treat the event;
- Toxicity Grade according to CTCAE 4.03 (Investigator to designate);
- Causality: relationship to study drug (Investigator to designate);
- Seriousness of the AE;
- The study period for AEs collection is defined as 30 days following the last administration of trial treatment unless the AE is unexpected and suspected to be related to the study treatment, in such case the AE should be reported regardless to the scope of reporting period.

13.3.7. Telephone Contact 24–32 Hours Post-treatment (visits 1-6)

- After each instillation, the patient will be given a questionnaire and requested to capture his/her post-treatment experience: first urination time, and remnant of gel in the urine (Appendix IV). Twenty-four (24 to 32 hours post each instillation, the patient will be contacted (via telephone) and answers for the questionnaire will be collected, and the questionnaire will be returned at the next visit. At this point, any spontaneously reported adverse events will also be recorded. If necessary, a patient may be called for an unscheduled visit to follow up on any post-treatment adverse event that requires clinical evaluation or follow-up.

13.4. LAB 1 (V7) & LAB 2 (V8):

One week and 3 weeks following the last of the weekly instillations, CBC (complete blood count), renal and liver function tests will be done for safety control. A deviation window of ±

3d is allowed.

These tests may be done in lab which is external to the hospital. In case of use of an external lab, the external lab's quality assurance documentation, normal ranges and CV of head lab must be collected by the site.

13.5. Primary Disease Evaluation Visit (PDE, V9)

5 weeks (± 1 week) Post last instillation.

Following completion of the instillation treatment series, a 5-week ± 1 week healing period prior to evaluation of treatment response and, if needed, performance of ureteroscopic resection of remaining UTUC lesions. At the PDE visit, the following activities will be performed:

- Review and recording of AEs and concomitant medication;
- Full physical examination and vital signs measurements (**Appendix I** and **Appendix II**);
- Blood tests and urinalysis (**Appendix III**);
- Urine culture (only when applicable);
- Pregnancy tests (for women with childbearing potential; **Appendix III**);
- Upper tract urine cytology (**Appendix III**) - The upper tract urine must be collected using a catheter (wash), **before** any biopsy or topical treatment was done.
- UUT lesions status, i.e., number of lesions, lesion size, location and morphology of remaining lesions (if any) will be assessed visually during the URS and documented in the patient's file. Document the lesions in the UUT Lesion Documentation Form;
- Biopsy or brush biopsy for histopathology for all remaining tumors if technically feasible;
- Evaluation of response (Section 14)
- Re-Evaluation of UTUC Treatment – Has UTUC treatment plan changed compared to prior entering the trial? N / Y, and planned treatment.

13.5.1. Complete Response (CR) patients

- For patients who demonstrate Complete Response (CR) evaluated by visual inspection via URS upper tract urine cytology will be performed to confirm no residual disease (See Section 9.2.1)
- Patient demonstrating CR at PDE will undergo a maintenance MitoGel™ treatment (refer to section 11.3.5).

13.5.2. Non-CR patients

- For patients who did not demonstrate CR, to the extent that it is possible, all remaining lesions will be biopsied. The patients shall undergo any additional surgical or other treatment the PI decides deem necessary to treat the patient. The tumor location, size and grade, as well as the surgical procedure or treatment provided to treat the remaining disease will be documented;
- If no lesion was detected via URS, but the UUT urine cytology from the upper tract is equivocal positive, patient will be re-evaluated by urine cytology prior to the next scheduled maintenance treatment (~3 weeks after the original cytology test at the PDE) and prior to the instillation on that day. If the urine cytology is negative, the patient will be considered as a CR. If repeated cytology results are positive or equivocal, patient will be considered as not having CR (i.e., CR = "failure"; see Section 9.2.1)

13.6. CR Patients Maintenance Instillations (Maintenance Visits)

A maintenance treatment will start immediately after the local lab confirms that patient's cytology is negative for cancer, and no longer than 3 weeks post PDE, unless there is a medical condition which requires postponing the treatment. In these cases, the first maintenance instillation should be delayed until recovery.

- Maintenance Regimen – MitoGel™ Admixture will be given once monthly (±1 week) until one month prior to last FU visit within the study (i.e., until Month 11 post PDE).
- Safety assessment – During maintenance treatment at each instillation the patients will have performed in the hospital local lab, safety lab tests, physical examination and vital signs per protocol (see **Appendix I - Appendix II**). For patients who drop out of the study safety will be assessed according to the SOC.

13.7. Follow-up Visits (V12, V15, V18, V21)

Follow up visits for patients who demonstrate CR will be performed 3, 6, 9, and 12 months following the PDE:

Allowed visit window deviation for each of the FU visits is ±2 wks.

The following activities will be performed:

- Review of unresolved AEs and recording of newly AEs (See Section 19 for management of AEs)

- Physical examination & vital signs, and laboratory tests required the investigator think are required for the follow up on any unresolved AEs, should be conducted at the discretion of the investigator or according to the Standard of Care (SOC)
- CTU (only in FU 12 months (V21)
- Blood tests and urinalysis (**Appendix III**)
- Pregnancy tests (for women with childbearing potential only)
- Upper tract washing urine cytology at every Follow-up Visit (**Appendix III**). The upper tract urine must be collected using catheter (wash), **before** any biopsy or topical treatment was done
- Review of concomitant medications

During FU period, patients will be followed-up for twelve months (12) or until disease recurrent or progression; however, during this period the following activities should be done:

- When done, histopathology results will be recorded in the patient's FU records,
- The presence of UUT lesions and status will be visually assessed during URS. Recurrence, progression (defined as increase in grade or stage), or durable CR (defined as NDD) will be determined for each patient
- Recurrence is to be confirmed by histopathology. To rule out recurrence biopsy of all visible lesions must be negative for urothelial carcinoma.
- Recurrence for the analysis purpose will only count the direct recurrence of the original treated area, meaning the upper urinary tract above the UGJ. Disease appearance/recurrence in other locations will be documented in the CRF, but will not be considered in this trial as a tumor recurrence.
- In case of disease progression in the UT during the follow-up period, the patient will be considered as a durable CR until the time of the progression findings. In case of recurrence or progression assessed during the FU period, the patient will be considered as having completed the trial and will not be summoned for further follow-up visits.

13.8. Unscheduled Visit

An unscheduled visit may be performed at any time during the trial if the investigator decides that the clinical state of the patient does not permit instillation of the IP, for assessment of safety, at the Patient's request, or as deemed necessary by the investigator. The date, reason, and procedures done in unscheduled visit will be recorded in the patient's file and the CRF.

13.9. Treatment Discontinuation

Treatment discontinuation prior to PDE

If a patient discontinues during the treatment period or at any time prior to the PDE Visit, the patient to complete PDE visit within 4+/-1 week of last instillation and perform all assessments of the PDE visit (Section 13.4);

If the patient appears to have CR at PDE, patient should continue FU within the trial receiving the maintenance treatments should be considered as well;

If patient agrees for FU within the trial or agrees to continue to share information regarding his/her disease status, information collected during the FU care of the patient should be recorded in the CRF.

Treatment Discontinuation during Maintenance

If patient discontinues during the maintenance period or at any time after PDE visit, an unscheduled visit should be done (one month after the last installation treatment), in which following activities should be performed:

- Full physical examination and vital signs measurements
- Blood tests and urinalysis
- Pregnancy tests (for women with childbearing potential)
- Review and recording of AEs and concomitant medication

If patient agrees to continue to share information regarding his/her disease status, information collected during the FU care of the patient should be recorded in the CRF.

14. Schedule of Events

14.1. Part I - All Patients - Up to PDE Visit

Study Week†	Wk (-)4-(-)1	Treatment period								Primary Disease Evaluation Wk 10 (±1 w)
		Wk 0	Wk 1 (±3 d)	Wk 2 (±3 d)	Wk 3 (±3 d)	Wk 4 (±3 d)	Wk 5 (±3 d)	Wk 6 (±3 d)	Wk 8 (±3 d)	
Visit Number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Visit Name	**Screening‡**	**Tx #1**	**Tx #2**	**Tx #3**	**Tx #4**	**Tx #5**	**Tx #6**	**Lab 1**	**Lab 2**	**PDE**
Informed consent	X									
Demographics	X									
General and Urothelial Carcinoma Medical History, Smoking	X									
Concomitant Medications Review	X	X	X	X	X	X	X			X
Eligibility criteria	X	X§								
Full Physical Examination	X									X
Urology oriented Physical Examination	X	X	X	X	X	X	X			X
Vital signs♠	X	X	X	X	X	X	X			X

† Time windows for study visits: V2-V6 ±3 day; V9 ±1 week
‡ Screening activities may be performed on separate days as long as they are completed within the screening period, before treatment starts.
§ Investigator and sponsor confirmation of eligibility prior to instillation. Entry into the trial will be based on the local pathologist diagnosis.
♠ Vital signs: Body temperature, blood pressure, heart rate, height and weight (screening)

Study Week†	Wk (-)4-(-)1	Treatment period						Wk 6 (±3 d)	Wk 8 (±3 d)	Primary Disease Evaluation Wk 10 (±1 w)
		Wk 0	Wk 1 (±3 d)	Wk 2 (±3 d)	Wk 3 (±3 d)	Wk 4 (±3 d)	Wk 5 (±3 d)			
Visit Number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Visit Name	**Screening‡**	**Tx #1**	**Tx #2**	**Tx #3**	**Tx #4**	**Tx #5**	**Tx #6**	**Lab 1**	**Lab 2**	**PDE**
CBC, liver and renal function, coagulation **	X	X♣	X♣	X♣	X♣	X♣	X♣	X coagulation not required	X coagulation not required	X
Urinalysis/dipstick	X	X	X	X	X	X	X			X
Urine culture	X	X††	X††	X††	X††	X††	X††			X††
CTU or MRI	X‡‡									
Biopsy for histopathology	X§§									X***
Upper Urinary Tract Urine cytology-washing	X§§									X
Pregnancy serum test †††	X	X‡‡‡	X‡‡‡	X‡‡‡	X‡‡‡	X‡‡‡	X‡‡‡			X‡‡‡
Pregnancy urine test †††		X	X	X	X	X	X			X

** If done one week prior to screening, acceptable. Treatment period- To be performed before the instillation, see Appendix III

♣ In case patient preformed all required blood test according to Appendix III up to 3 days prior to the instillation- no need to repeat;

†† To be performed when UTI is suspected according to urinalysis results.

‡‡ CTU to be repeated if done more than 3 months prior to first treatment. In the event that CTU is not applicable from any reason, an MRI should be performed instead

§§ Histopathology and cytology evidence of LG UTUC performed ≤2 months prior to V0 (or 3 months prior to the first instillation) is acceptable provided that the slides can be sent for central pathology evaluation. All Histopathology evaluations performed locally will be reviewed centrally.

*** Biopsy will be taken at PDE and any follow up visit when lesions are detected and recurrence is suspected.

††† Only for women of childbearing potential

‡‡‡ Only for women of childbearing potential and a positive pregnancy urine test

Study Week†	Wk (-)4-(-)1	Treatment period						Wk 6 (±3 d)	Wk 8 (±3 d)	Primary Disease Evaluation Wk 10 (±1 w)
		Wk 0	Wk 1 (±3 d)	Wk 2 (±3 d)	Wk 3 (±3 d)	Wk 4 (±3 d)	Wk 5 (±3 d)			
Visit Number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Visit Name	**Screening‡**	**Tx #1**	**Tx #2**	**Tx #3**	**Tx #4**	**Tx #5**	**Tx #6**	**Lab 1**	**Lab 2**	**PDE**
Ureteroscopy (URS)+C arm	X§§§									X
Recording/ Photographing of UUT lesions number, size, appearance and location	X									X
Volumetric estimation (retrograde pyelography and fluoroscopy) 3 repetitions	X									
Provide prescription for sodium bicarbonate, Prophylaxis antibiotic, anti-histaminic and diazepam(optional) and written instructions	X									
Patient card, letter to GP, Guidance letter to patient	X									
Fluoroscopy		X	X	X	X	X	X			
Cystoscopy for catheterization		X	X	X	X	X	X			
MitoGel™ Admixture administration		X	X	X	X	X	X			

§§§ URS to be repeated If done more than 2 months prior to V0, or in case it is not informative enough for the trial. In case URS cannot be performed, other method may be used for baseline lesion/s mapping

Study Week†	Wk (-)4-(-)1	Treatment period						Wk 6 (±3 d)	Wk 8 (±3 d)	Primary Disease Evaluation Wk 10 (±1 w)
		Wk 0	Wk 1 (±3 d)	Wk 2 (±3 d)	Wk 3 (±3 d)	Wk 4 (±3 d)	Wk 5 (±3 d)			
Visit Number	**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Visit Name	**Screening‡**	**Tx #1**	**Tx #2**	**Tx #3**	**Tx #4**	**Tx #5**	**Tx #6**	**Lab 1**	**Lab 2**	**PDE**
VAS for pain evaluation		X	X	X	X	X	X			
6 hours observation post treatment		X								
1.3 gr × 3 of sodium bicarbonate (|The night before, morning of and 30 min. prior to treatment)		X	X	X	X	X	X			
MMC level (plasma) ****		X ††††								
Phone reminder day prior to instillation: Bicarbonate, liquid limitation, diuretics,		X	X	X	X	X	X			
Supply questionnaire for 24-32 h Post treatment telephone contact‡‡‡‡		X	X	X	X	X	X			
24-32 h Post treatment telephone contact ‡‡‡‡		X	X	X	X	X	X			
Adverse Events	X	X	X	X	X	X	X			X §§§§

**** In 6 treated patients
†††† Prior to instillation, 30min., 1, 2, 3, 4, 5, and 6 hours post instillation
‡‡‡‡ For patients treated in retrograde fashion only
§§§§ Review of unresolved AEs and recording of newly emerging AEs considered to be related to participation in the study (See Section 19)

Part II –Maintenance & Follow Up - Complete Response Patients

Study Month*****	**Maintenance Treatment (±1 w)**											
	up to 3 Weeks post PDE		**FU1 +3mo Post PDE (±2 w)**			**FU2 +6mo Post PDE (±2 w)**			**FU 3 +9mo Post PDE (±2 w)**			**FU 4 +12mo Post PDE (±2 w)**
Visit Number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**
Visit Name	**Maint. #1**	**Maint. #2**	**Maint. #3**	**Maint. #4**	**Maint. #5**	**Maint. #6**	**Maint. #7**	**Maint. #8**	**Maint. #9**	**Maint. #10**	**Maint. #11**	**FU4 Trial Completion**
Urology oriented Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
CBC, liver and renal function, coagulation††††††	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis/dipstick	X	X	X	X	X	X	X	X	X	X	X	X
Urine culture‡‡‡‡‡	X	X	X	X	X	X	X	X	X	X	X	X
CTU Scan												X§§§§§
Biopsy for histopathology******			X			X			X			X

***** Time windows for study visits V10, V12, V15, V18, V21 ±2 weeks.
†††††† CBC, liver and renal function, coagulation tests to be performed before the instillation, see Appendix III
‡‡‡‡‡ To be performed when UTI is suspected according to urinalysis results
§§§§§ At the 12 M FU Visit, CT scan should be obtained for all patients who continue to demonstrate CR
****** Biopsy will be taken at PDE and any follow up visit when lesions are detected and recurrence is suspected.

Study Month*****	Maintenance Treatment (±1 w)											
	up to 3 Weeks post PDE		FU1 +3mo Post PDE (±2 w)			FU2 +6mo Post PDE (±2 w)			FU 3 +9mo Post PDE (±2 w)			FU 4 +12mo Post PDE (±2 w)
Visit Number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**
Visit Name	**Maint. #1**	**Maint. #2**	**Maint. #3**	**Maint. #4**	**Maint. #5**	**Maint. #6**	**Maint. #7**	**Maint. #8**	**Maint. #9**	**Maint. #10**	**Maint. #11**	**FU4 Trial Completion**
Upper Urinary Tract Urine cytology-washing			X			X			X			X
Pregnancy urine test ††††††	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy serum test ‡‡‡‡‡‡	X	X	X	X	X	X	X	X	X	X	X	X
Ureteroscopy (URS)			X			X			X			X
Recording/Photographing of UUT lesions number, size, appearance and location			X			X			X			X
Fluoroscopy	X	X	X	X	X	X	X	X	X	X	X	
Cystoscopy for catheterization	X	X	X	X	X	X	X	X	X	X	X	
MitoGel™ Admixture instillation	X	X	X	X	X	X	X	X	X	X	X	
1.3 g × 3 of sodium bicarbonate	X	X	X	X	X	X	X	X	X	X	X	

†††††† Only for women of childbearing potential
‡‡‡‡‡‡ Only for women of childbearing potential and a positive pregnancy urine test

Study Month*****	Maintenance Treatment (±1 w)											
	up to 3 Weeks post PDE		FU1 +3mo Post PDE (±2 w)			FU2 +6mo Post PDE (±2 w)			FU 3 +9mo Post PDE (±2 w)			FU 4 +12mo Post PDE (±2 w)
Visit Number	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**	**V19**	**V20**	**V21**
Visit Name	**Maint. #1**	**Maint. #2**	**Maint. #3**	**Maint. #4**	**Maint. #5**	**Maint. #6**	**Maint. #7**	**Maint. #8**	**Maint. #9**	**Maint. #10**	**Maint. #11**	**FU4 Trial Completion**
Phone reminder day prior to instillation: Bicarbonate, liquid limitation, diuretics	X	X	X	X	X	X	X	X	X	X	X	
Review of Disease Outcome and Complete Response Durability			X			X			X			X
Adverse Events /Concomitant Med.	X	X	X	X	X	X	X	X	X	X	X	X

15. Evaluation of Response

Patient response will be evaluated according to the following criteria:

Complete Response (CR): A patient will be considered to have had CR if there is no detectable disease (NDD). To determine NDD, the following conditions should be fulfilled (see also Figure 1 in Section 9.2.1)

1. If visual assessment (URS) indicates no remaining tumors the upper tract urine cytology must be negative;
2. If tumors are visible during URS, all remaining and accessible tumors should be biopsied. If the biopsied tumors are not viable upon histopathological evaluation and the cytology is negative, the patient should be considered to have had CR;
3. In a case where the preferable treatment is RNU and its pathological evaluation indicates that no viable tumor(s) remained in the affected kidney (e.g., non-viable lesion), the patient will be considered CR retroactively.

No Complete Response (NCR): A patient will be considered to have had NCR if there is a residual disease. NCR should be determined only after pathology result was received from the pathology local lab.

Table 2 Response: Classification in possible scenarios (Assessed at PDE Visit)

Visual Assessment via Video-URS	Biopsy (central lab)	Cytology (central lab)	CR Yes/No
Negative	NA	Negative	Yes (Success)
Negative	NA	Equivocal positive	No*
Negative	NA	positive	No (Failure)
Positive	Positive	Negative	No (Failure)
Positive	Negative	Negative	Yes (Success)

* Unless at next maintenance the upper tract urine cytology is negative

15.1. Tumor Measurements and Classification of Partial Response (PR)

At Baseline, during the diagnostic ureteroscopy, the size of all measurable tumors for each patient will be estimated and recorded. Each measurable lesion will be identified with a unique identifier number, and the morphology and location will be recorded on a diagram of the upper urinary tract provided in the chart and CRF. Tumors size will be recorded in one dimension (the

longest diameter; mm). Measurable tumors are defined as those for which a reasonable visual estimation can be obtained visually and photographically. At PDE, the size of all measurable tumors identified at baseline, if still present, should be recorded, using the same identifier tumors number and location as recorded at baseline. PR is every change in the tumor size or number which is not CR or NR.

15.2. Assessment of UC Tumor Progression

Diagnosis of UC at the PDE visit with an increase in stage or grade compared to baseline will be tracked; however, as is explained below, it likely does not represent true progression for the following reasons:

1. Following RNU, a high rate (> 33%) of change in grade and stage of UC compared with the initial diagnostic biopsy has been reported [Smith, 2011). This is likely due to the poor specimens usually obtained during initial diagnostic URS. Therefore, if a patient diagnosed at Baseline with LG non-invasive UC and at the PDE with HG, or the tumor is found to be more invasive (stage increase); this more likely represents under grading/ under staging at the time of first diagnosis rather than true tumor progression;
2. The overall risk of progression for patients with LG papillary UC is about 5%. A 12-week interval, during which the patient is exposed to MMC treatment, is not generally considered long enough for progression to occur in patients with non-invasive urothelial carcinoma;

Upstaging/upgrading detected at the PDE visit will be recorded and the overall incidence will be compared with that reported in the literature. The progression of the initial disease during the FU period after the patient already achieved CR will be documented in the CRF.

15.3. Assessment of UC Tumor Recurrence

Follow up will be conducted for patient who were defined as CR at PDE, or for patients for whom the investigator was uncertain of the final diagnosis and chose to continue to the next FU visit for re-assessment.

Starting with the FU 1 visit (3 months post PDE visit), information regarding disease status based on Ureteroscopy, Upper tract washing urine cytology, and Biopsy, if needed, as well as intervention should be recorded. For a patient to be defined as having recurrence complete documentation should be obtained and the following criteria should be met:

- Visual confirmation of tumor presence; AND

- Positive biopsy for UC where it is technically feasible.
- Only recurrence in the treated area will be counted for the analysis as treatment failures. A new lesion within the renal pelvis be considered recurrent disease (meaning a disease recurrent in the UPJ and up). The appearance of urothelial carcinoma during the follow-up period in another area in the urinary system (the other kidney, ureter, bladder, and urethra) will be documented but will not be considered as a recurrence for the trial primary analysis.
- In a patient which during the trial period has a UC recurrence in the bladder and is required to undergo a TURBT, the surgery can be done during the FU period, and as long as his treatment doesn't require intravesical instillations the patient can stay in the FU with the maintenance treatment for his UTUC disease.
- If the recurrent bladder cancer in the FU period requires full course of intravesical treatment, it is the PI discretion whether to keep the patient in the FU period without the MitoGel maintenance treatment for the UT during the 6 weeks of the bladder instillations.
- If the recurrence is in the other kidney, and the patient requires immediate intervention, the FU period may be terminated for this patient and the durability will be calculated based on the existing data (depending also on the planned kidney surgery).

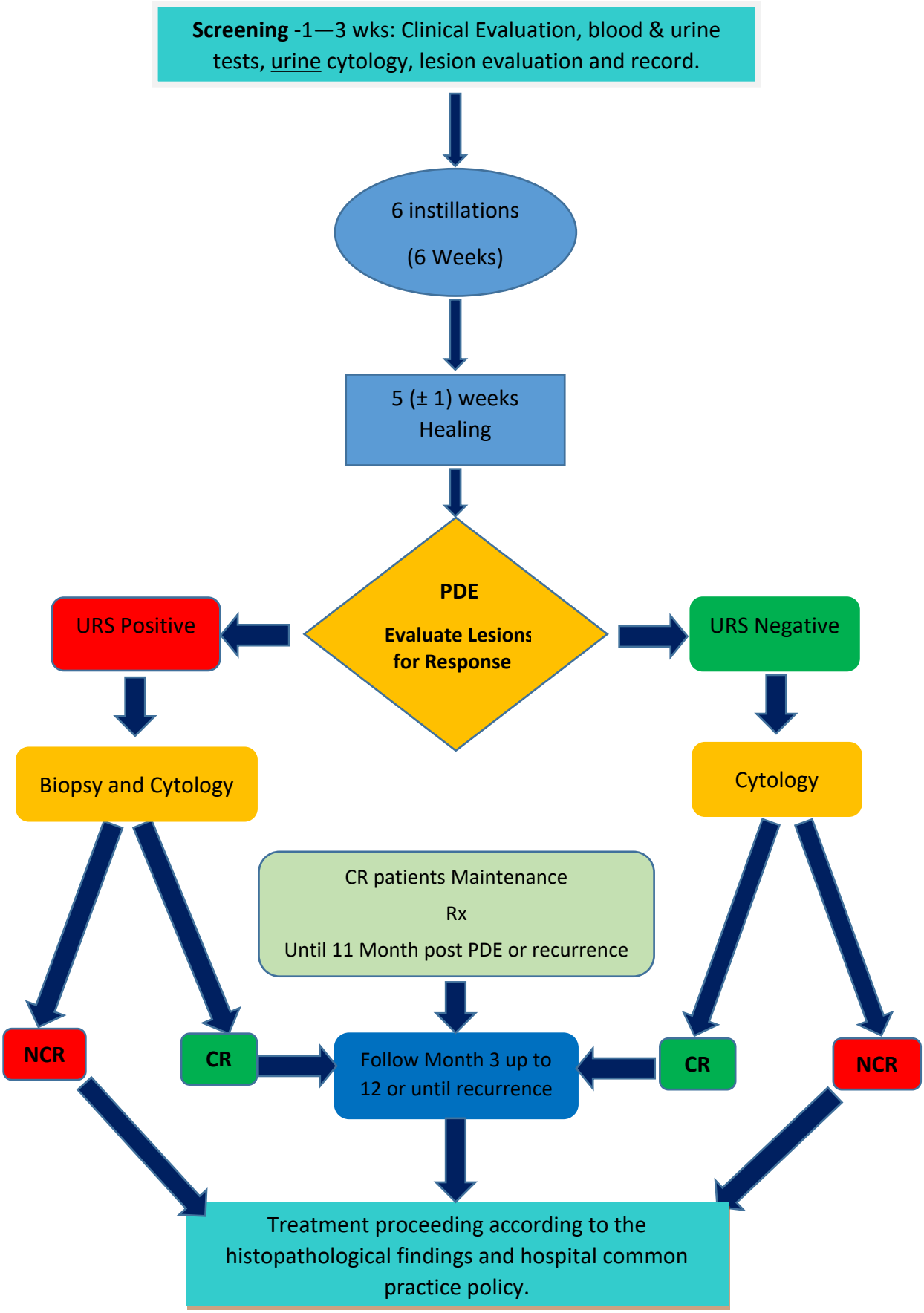
15.4. Pathological Evaluation:

Biopsies and upper tract washing urine cytology specimens obtained at baseline should be evaluated by the local institutional pathologist. Patient's enrollment to the trial will be based on the local pathologists' diagnosis.

A central pathology service will be used for this trial. Biopsy and urine cytology slides obtained either at Screening/Baseline, PDE and every FU visit, will be read by the central pathologist. The diagnosis based on local reading will be considered the final one for the purpose of primary efficacy evaluation.

Note: *Further details on the process will be provided in the Administrative Binder of the trial procedures.*

16. Trial Flow-Chart Per Patient



17. Patients Withdrawal From Treatment or/and Follow Up, and Trial Completion

A patient's preterm withdrawal from the treatment or from the trial can take place at any stage prior to trial completion, and in any case, in which emerging adverse events are of such a nature that the risk/benefit ratio is unacceptable to the individual patient.

17.1. Criteria for Patient withdrawal from MitoGel Treatment:

The single most important reason for premature discontinuation should be marked on the End of Treatment Form, under one of the following categories:

- Adverse Event/Serious Adverse Event
- Mandatory criterion for discontinuation per protocol
- Patient wishes to withdraw his/her consent for participation in the trial;
- Patient's non-compliance with treatment or protocol requirements;
- Patient lost to FU;
- Pregnancy.

17.1.1. Discontinuation from MitoGel Treatment is mandated in the following event:

a. Grade 4 neutropenia lasting >5 days

b. Febrile neutropenia

c. Grade 4 thrombocytopenia

d. Grade 3 thrombocytopenia with hemorrhage

e. Dose delay of >4 weeks due to an adverse reaction

f. Grade 3-4 non-infective cystitis

g. Grade 3-4 hematuria

h. Any grade of urinary system perforation

i. Any Grade 4 non-hematologic toxicity EXCEPT:

I. Grade 4 vomiting/diarrhea lasting <72 hours in the absence of maximal medical therapy

II. Grade 4 laboratory abnormalities that can be readily corrected and do not result in hospitalization

Note: No dose modifications or delays are allowed in patients who do not tolerate MitoGel

17.1.2. FU of Patients That Withdrew from MitoGel Treatment

For a patient who completes at least one instillation but withdraws from the treatment prior to the 6th instillation, the patient should be invited for an unscheduled visit in which all assessments scheduled for the PDE visit should be conducted. If the patient is classified as CR., the patient will be asked to continue providing follow up data during FU visits, which are similar to the ones conducted under the standard of care. Regardless, the site should explain to the patient the importance of continuing FU for disease management.

PDE will be performed 5 weeks (±1w) after last treatment, and all other FU procedures (safety and recurrence) will continue according to protocol. The patient's follow-up data will be collected in the trial database, upon completion of the trial (or an early withdrawal from the trial). In case of tumor recurrence, the patient's participation in the trial will be terminated.

If a patient withdraws from the interventional portion of a trial and does not consent to continue FU or provide clinical outcome information, the investigator must not access for purposes related to the trial the patient's medical record or other confidential records requiring the patient's consent. However, an investigator may review trial data related to the patient collected prior to the patient's withdrawal from the trial for the purpose of clinical management of the patient, and may consult public records, such as those establishing survival status.

17.1.3. Patients Withdrawal from the Trial

A patient will be withdrawn from the trial for any of the following reasons:

- Lost to follow-up;
- Withdrawal of consent;
- Sponsor terminates the study;
- Death.

If a patient is lost to follow-up, any reasonable effort must be made by the trial site personnel to contact the patient and determine the reason for discontinuation/withdrawal. Attempts to contact the patient must be documented in the patient's file (at least 3 documented attempts). If a FU visit was performed, relevant measures taken must be documented in the source document and entered into the CRF.

When a patient withdraws before completing the trial, the reason for withdrawal is to be documented in the source document and entered into the CRF.

In case of death at any trial time point throughout the trial FU period, the cause of death will be reported to the Ethics Committee.

17.2. Definition of Trial Completion

A patient will be considered to have completed the trial in the following cases:

- Patient was defined as PR or NR to treatment at PDE visit;
- For patients with CR at PDE, FU will continue until one of the following occurs:
  - Recurrence of tumor has occurred,
  - Patient has completed 12 months FU visit.

17.3. Replacement of Individual Patients

Patients who discontinued treatment will not be replaced. Ineligible (screen-failures) patients, or patients who did not receive any study medication will be replaced. Screen failed patient can be re-screen if he meets the criteria later on the study period. Screen Failures Minimal Required Data

The minimal required CRF forms for screen failure patients are:

- Demographics
- Inclusion Criteria
- Exclusion Criteria
- Patient Eligibility by site investigator
- Patient Eligibility by sponsor.

18. Statistical Methodology

At least 74 evaluable patients meeting all inclusion and exclusion criteria with a confirmed diagnosis of LG UTUC will participate in this trial to provide 88.5% power to demonstrate efficacy (See Section 18.2). Assuming a lost to follow-up rate of about 10%, approximately 83 subjects will participate in this trial. While no formal, interim analysis for stopping the trial for success is planned, the trial's DMC will have continuous access to safety and efficacy data. This is meant to:

a. Enable carrying out the following FDA suggestion: "The agency clarified that the sponsor does not have to wait until all patients have completed this additional follow up before submitting the application. The sponsor can submit an application once they believe they have demonstrated safety and efficacy of this product." (PIND Nov, 2015 meeting minutes, p. 7).

b. Avoid operational bias by providing the access to cumulative ongoing trial data to an independent body only.

The DMC will have the authority to decide whether the data is sufficiently indicative of safety and efficacy for submission to FDA even before the complete sample has been recruited and/or followed up. At the same time, even if UroGen provides interim data to FDA at DMC's recommendation, the study will continue to enroll subjects as per study plan while discussions with the FDA are taking place.

It should be noted that MitoGel is intended for treating the *entire* upper urinary tract, not only a single marker lesion. Thus, subjects with multiple lesions will be included in the study and treatment will be considered successful only if all lesions disappear.

This study will test one primary and one key secondary efficacy endpoints. The former relates to CR at PDE visit while the latter assesses durability of CR at 12 months (for those demonstrating CR at PDE). To control Alpha for Type I Error, hypotheses will be tested hierarchically—primary first and key secondary, second—and only a significant result on the first test will enable conducting the second hypothesis test. Consequently, Alpha will be 0.05 two sided for both tests.

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

18.1. Significance Level

The overall significance level for testing primary efficacy is 0.05, two sided. Since there is no formal interim analysis (DMC's independent review of the data is described in Section 18), and Alpha is controlled for multiple testing hierarchically, Alpha for statistical testing will be 0.05, two sided. Non-confirmatory analyses will not control for multiple testing so that Alpha for significance in each will remain 0.05, two-sided.

18.2. Sample Size Rationale

Sample size determination was performed under the following assumptions:

- The primary efficacy endpoint of the trial is the Complete Response (CR) rate at the PDE Visit;
- It is expected that the true CR rate following treatment with MitoGel™ is 30% or more;
- The principal analysis of the primary endpoint will aim to rule out a threshold rate of 15% using a two-tailed exact test for binomial proportion at two-sided Alpha = 0.05; i.e., 15% CR is the study's performance goal (PG).

Under these assumptions, a sample of 74 evaluable patients will provide a power of 88.5% to demonstrate that the observed CR rate is superior to the PG of 15%. Assuming a lost to follow-up rate of about 10%, at total of about 83 subjects will participate in this trial.

It should be noted that this trial is not powered for the key secondary endpoint.

18.3. Futility Analysis

A futility analysis is planned for this trial after 20 evaluable subjects have provided primary efficacy data at the PDE visit or after as applicable[24]. Since this interim analysis will be for futility only (i.e., it will not provide the option of stopping for success). Alpha remains unaffected and need not be adjusted for multiplicity.

Futility will be declared if the conditional power for success at the end of the trial given results at N = 20 is below 25% (i.e., less than 1 CR case out of 20). It should be noted that the choice of futility analysis after 20 subjects was made based on: a) Company's wanting to analyze the data as early as possible, so as not to conduct a larger trial that is futile and b) Error of Type II, Beta, at N = 20 and the above rule for futility is 0.0; i.e. this futility analysis does not reduce overall study power. Results of the futility analysis will be presented in closed session to the DMC, which will make the final determination of trial continuation based on the statistical and clinical considerations.

18.4. Analysis Sets

18.4.1. Safety Analysis Set

The safety analysis set will consist of all patients who enrolled in the trial and received at least 1 instillation of MitoGel™ Admixture. This analysis set, which will include all data captured in data base for these patients, will serve as the primary analysis set for safety assessment. Intent-to-Treat (ITT) Analysis Set (=safety analysis set).

This analysis set, which will include all data captured in the database for these patients, will serve as the primary analysis set for the primary efficacy analyses and inference.

[24] Equivocal primary efficacy results at PDE visit (e.g., cytology = "equivocal"), will require follow-up testing for final determination of primary endpoint (see Section 9.2.1).

- **Treatment of Missing Values in ITT:**

ITT subjects with no observed value on primary efficacy will be imputed primary efficacy failures. Note that this only include patients who dropped from the study for any reason before the PDE evaluation. At the same time, sensitivity analyses will evaluate the robustness of results to different assumptions of missingness.

Treatment of missing values for the secondary endpoint detailed in Section18.7.2.

18.4.2. Local Modified Intent-to-Treat (mITT) Analysis Set

The local modified intent to treat (local - mITT) analysis set will be a subset of ITT subjects with confirmed LG UTUC at Screening by *local* lab and who arrived to the PDE evaluation.

Missing values: Only observed values will be used in local - mITT; i.e. missing data will not be imputed.

18.4.3. Central Modified Intent-to-Treat (mITT) Analysis Set

The central modified intent to treat (Central - mITT) analysis set will be a subset of ITT subjects with confirmed LG UTUC at Screening by *central* lab and who arrived to the PDE evaluation and received the central lab diagnostic.

Missing values: Only observed values will be used in central - mITT; i.e. missing data will not be imputed.

18.4.4. Per Protocol (PP) Analysis Set 1

The Per Protocol (PP) analysis set is a subset of the Local mITT Analysis Set and will consist of all enrolled patients who received at least 4 MitoGel™ Admixture instillations and have observed data on the primary efficacy endpoint. Patients who are identified as HG at the PDE visit will be excluded from the PP1 population. This analysis set will include all data captured in database for this subpopulation.

18.4.5. Per Protocol (PP) Analysis Set 2

The Per Protocol (PP) analysis set is a subset of the Local mITT Analysis Set and will consist of all enrolled patients who received a total of 6 MitoGel™ Admixture instillations, who do not have major protocol violation, and have observed data on the primary efficacy endpoint. Patients who are identified as HG at the PDE visit will be excluded from the PP2 population. This analysis set will include all data captured in database for this subpopulation.

18.4.6. Complete Responders at the PDE Visit (PDE_{CR}) Analysis Set

The PDE_{CR} analysis set is a subset of the ITT Analysis Set who had a Complete Response (CR) at the PDE Visit.

18.5. Patient Disposition

Subject disposition will be tabulated; the number of enrolled, exposed, prematurely terminated and completed subjects will be summarized separately according to treatment and by visit (where relevant). A list of dropouts will be prepared including reason for discontinuation, and time of discontinuation.

18.6. Demographic and Baseline Characteristics

Demographics and baseline data as well as disease prognostic factors, medical history, and prior medications will be summarized using the safety analysis set by descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation (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 separately if necessary.

18.7. Efficacy Analyses

18.7.1. Primary Efficacy Analyses

The principal analysis of the primary endpoint will test the Complete Response (CR) rate defined as percent of patients with CR at the PDE Visit or necessary follow-up (See Section 9.2.1) using the ITT Analysis Set. Patients who did not demonstrate confirmed CR at PDE visit or necessary follow-up will be considered for the purpose of this analysis as treatment failures.

The primary efficacy analysis will test the following hypotheses.

H_0: $CR_{rate} \leq 15\%$

H_1: $CR_{rate} > 15\%$

Testing will be done by using an exact binomial two-sided hypothesis testing, with two-sided Alpha = 0.05. (Note that this is in fact identical to the one-sided testing with Alpha=0.025). In addition, exact binomial 95% confidence interval about the observed CR_{rate} will be provided.

It should be noted that FDA has made allowance for data assessed qualitatively by the DMC being submitted for the Agency's evaluation (see Section 18) that, in FDA's opinion, may be sufficient for demonstrating safety and efficacy of the product.

18.7.2. Sensitivity Analysis for the Principal Analysis of the Primary Endpoint

The following analyses will be done to examine the robustness of the study's primary conclusion to inclusion criteria and differing patterns of missingness. The primary analysis described in the previous section will be repeated using

- Local diagnosis in Local-mITT, PP1, PP2 populations
- Central diagnosis in Central-mITT

In addition, two alternative imputation methodologies will be examined in the ITT population.

1. Tipping point
   In this analysis missing values on CR will be progressively imputed "failure" until such point when the CR rate is no longer significant; i.e. the 95% confidence interval about CR rate is no longer wholly above 15%. The point at which results are no longer significant will be defined as the "tipping point." (Recall that missing subjects in ITT are imputed "failure" for the primary analysis, which is essentially a worst case analysis.)
2. Multiple Imputation
   The missing response status will be imputed using the multiple imputation procedure (PROC MI in SAS®). Ten (10) imputed datasets will be created. The imputation model will use the following covariates: Sex, Age, number of papillary lesions at screening, the largest diameter at Screening, Tumor Burden and total number of episodes.

18.7.3. Key Secondary Efficacy Analysis: Long Term Durability of CR

The study's key secondary endpoint is durable response at 12-month follow-up in the CR analysis set, which will test the following hypotheses:

H_0: $CR_{12\text{-months}} \leq 40\%$

H_1: $CR_{12\text{-months}} > 40\%$

The key secondary endpoint will be tested by constructing a two-sided, 95%, Exact Binomial confidence interval about the rate of subjects in the CR analysis set continuing to show CR at 12 months. We will declare success on this endpoint if the lower bound of the confidence interval is above 40%.

The key secondary endpoint will be tested on 12-month data, where missing data due to:

- Discontinuation due to AEs related or probably related to investigational therapy = "failure"
- Discontinuation or lost-to-follow-up for any other reason will not be imputed

Since Alpha for multiple testing is controlled using the hierarchical method, there is no need to adjust Alpha for the key secondary endpoint.

Observed rate of CR at 12 months was selected because of its clinical meaningfulness. At the same time, the continuous durability of CR will also be analyzed by Kaplan Maier analysis. Durability will be defined from the time of the PDE visit where first CR is confirmed until the first visit where a patient do not meet the definition of CR. Patients who discontinued the study for any reason will be censored at their last assessment in which they had maintained a complete response.

18.7.4. Sensitivity Analysis for the Dichotomous Key Secondary Endpoint

For dichotomous key secondary analysis, patients who did not arrive the last FU visit and have no prior recurrence, are treated as Failures (which is the "worst case" imputation scenario). Sensitivity analysis will be done to examine the results if alternative imputation scenarios are used. Specifically, the tipping point imputation will be applied.

In this analysis we begin by imputing all missing subjects (early terminations) "Success" (or CR). Then, at each step, number of imputed "Successes" will reduce by one and number of imputed "Failures" will increase by 1, until the case where all missing values are imputed "Failure" (which is equivalent to the primary analysis). For each imputation scenario, exact binomial hypothesis testing p-value will be reported.

In addition, to the described above, analysis where only observed data is used will be done.

18.7.5. Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted using all but the safety analysis sets.

Durable CR at 3, 6 and 9 months will be analyzed using the CR analysis set, so that the denominator for CR rate consists only of those subjects demonstrating CR at PDE.

Durable CR at 3, 6 and 9 months will be analyzed by constructing a two-sided, 95%, exact binomial confidence interval about CR rate. Subjects whose data are missing at 3, 6 and 9 months due to AEs definitely or probably related to treatment will be imputed failures. Subjects whose status of CR is missing at some FU visit, but the CR is confirmed at any further FU visit will be imputed CR (Success) backward. Data missing for other reasons will be excluded from the analysis.

For patients with PR at PDE visit, originally planned and actually received UTUC treatment will be compared.

18.8. Evaluation of Safety

Safety analyses will be descriptive and narrative in nature, with SAE's and AE's coded using MedDRA Version 19.0 or higher and tabulated by body system, preferred term, severity and relation to study drug and procedure. Descriptive statistics will be provided over time as appropriate.

18.8.1. Adverse Events

Adverse events will be recorded from the time a patient has signed the Informed Consent. Adverse Events (AEs) reported by the investigators will be coded according to the MedDRA dictionary.

The following will be incorporated into the analysis of adverse events:

- All analyses to be provided will include coded AEs;
- Adverse events analyses will include only Treatment Emergent Adverse Events (TEAEs), namely, those events which started on the day of first trial IP administration or afterwards. Listings of both TEAEs and non-TEAES will be provided;
- The incidence (no. of patients) and frequency (no. of events) of TEAEs will be provided when broken down by System Organ Class (SOC) and by Preferred Term (PT) according to MedDRA dictionary;
- Breakdowns of TEAEs by all AEs attributes will also be provided;
- Breakdowns of TEAEs by age, sex and volume of instillation will also be provided;
- The derived dictionary used in the analyses displaying the MedDRA System Organ Class (SOC), the Preferred Term (PT), and the AE Verbatim Term as specified by the Investigator, will be provided;
- The incidence (no. of patients) and frequency (no. of events) of serious TEAEs will be provided when broken down by System Organ Class (SOC) and by Preferred Term (PT) according to MedDRA dictionary as well as by SAEs attributes and by age, sex, and volume of instillation. SAEs will also be listed.

18.8.2. Safety Laboratory Tests

Analyses of safety laboratory data will be performed in the following manner:

- Graphical presentation given in mean values + 2 standard errors of the mean of laboratory tests results by scheduled visits will be provided as well;

- 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 potentially clinically significant (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 lab values as well as the individual patient listing will be provided using the denominator which is the number of patients with at least one post-baseline administration of trial medication. Individual patients' listings of PCS measurements will also be presented.

18.8.3. Vital Signs

Analyses of vital signs (blood pressure, pulse, temperature, and respiration rate) will be performed in the following manner:

- Descriptive statistics of vital signs before first trial instillation and during trial as well as the changes from baseline by scheduled visit will be displayed;
- The incidence (no. of patients) of potentially clinically significant (PCS) abnormal values will be summarized in a frequency table using the criteria defined by the Sponsor before first trial instillation. Please note that the denominator to be used for calculating percentages is the number of patients with at least one post-baseline evaluation. The incidence tables as well as the individual patient listing of vital signs of PCS will be reported.

18.8.4. Physical Examination

Any clinically relevant changes occurring from screening until the last trial visit will be recorded in the Adverse Event Sections of the CRF.

18.8.5. Tolerability Assessments

Tolerability analysis will be based on the number and percent of patients who failed to reach the PDE visit due to related adverse events (probably, definitely) and overall discontinuation rate. The time to withdrawal due to adverse events and overall discontinuation rate, starting from first trial instillation censored by the date of the PDE visit, will be presented using Kaplan-Meier curves.

A similar analysis approach will be repeated for the FU1 and FU4 visits.

18.8.6. Use of Concomitant Medications

The WHO drug dictionary will be used to classify medications verbatim for Concomitant Medication 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 trial first instillation. An incidence table including patient counts (no. of patients) and percentages broken down by Medication Class and Preferred Term will be provided;
- Concomitant Medications Use (Post-First Trial Instillation): Analyses will include only coded medications that were consumed following the first trial instillation, regardless if drug initiation date was before or after first trial instillation. An incidence table including patient counts (no. of patients) and percentages broken down by Medication Class and Preferred Term will be generated;
- Prohibited Medications: systemic chemotherapy, intravesical chemotherapy (full course) and BCG, which is part of the exclusion criteria.

18.8.7. MMC Levels (Pharmacokinetics) Profiling

Pharmacokinetic (PK) profile during the 6 hours following the first administration of MitoGel™ will be based on PK sampling at 0, 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 MitoGel™ 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 MitoGel™ 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, this data, combined with data emerging from other trials/compassionate use program may be used in population pharmacokinetic model development and analysis.

19. Management of Adverse Events

19.1. Definitions

19.1.1. Adverse Events

Adverse Event (AE): Any untoward medical occurrence in a patient or in a clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory, physical exam, 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 adverse event shall be examined by a doctor as soon as possible, making whatever 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. 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.

Adverse Drug Reaction (ADR)/ Adverse Procedure Reaction: Any noxious and unintended responses to a medicinal product/procedure, related to any dose administered. The phrase responses to a medicinal product/procedure, means that a causal relationship between a medicinal product/procedure, and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out ("Note for Guidance on Good Clinical Practice" CPMP/ICH/135/95). The definition also covers the medication errors and uses outside what is foreseen by the trial protocol, include misuse and abuse of the product.

19.1.2. Serious Adverse Events

A "**serious adverse event (SAE**) is any untoward medical occurrence or effect that at any dose:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity; or
- Is a congenital anomaly/birth defect.

These characteristics/consequences have to be considered at the time of the event; some medical events may jeopardize the patient or may require an intervention to prevent one of above characteristics/consequences. Such events (hereinafter referred to as an **"important medical**

events") should also be considered as "serious" in accordance with the definition ("Note for Guidance on Good Clinical Practice" CPMP/ICH/135/95).

A **"non-serious adverse event** is an AE which does not meet the above criteria.

19.1.3. Suspected Unexpected Serious Adverse Reaction/Unexpected Adverse Drug Reaction (SUSAR /UADR):

UADR

An "Unexpected Adverse Drug Reaction" (UADR) is any noxious and unintended response that is related to the administration of an investigational product that has not been reported as expected in this protocol or the Investigator's Brochure, either from previous clinical studies or the non-clinical studies.

SUSAR/SUADR

A "Suspected Unexpected Serious Adverse Reaction" is any UADR that at any dose also meet the criteria of SAE above.

19.1.4. Causality

The investigator will determine the association between adverse event and treatment/procedure based on the following definitions:

- **Definitely Related**

A clinical event, including laboratory test abnormalities, which follows the administration of a medicinal product, over a reasonable time period, but which cannot be explained by a concomitant illness or by other medicinal products. The reaction must have already been observed for the suspected medicinal product. The reaction must improve with "de-challenge" and reappear with "re-challenge".

- **Probably Related**

A clinical event, including laboratory test abnormalities, which follows the administration of a medicinal product, over a reasonable time period, but which cannot be explained by a concomitant illness or by other medicinal products and the "de-challenge" response of which is clinically acceptable. "Re-challenge" data are not necessary.

- **Possibly Related**

A clinical event, including laboratory test abnormalities, which follows the administration of a medicinal product, over a reasonable time period, but which could also be explained by a concomitant illness or by other medicinal products. Information on suspension of the medicinal product may be missing or uncertain.

- **Not Related**

A clinical event, including laboratory test abnormalities, where the duration of which, after administration of a medicinal product, makes the causal relationship improbable and where other medicinal products or pre-existing conditions offer plausible explanations.

19.1.5. AE Intensity

The intensity of AE is to be graded by the investigator according to CTCAE 4.03 criteria, as outlined below:

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).

19.2. Reporting procedures

19.2.1. Instructions for Trial Personnel Regarding Patient Adverse Events 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.

19.2.2. Events Requiring Immediate (24 hours) Reporting

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

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

The investigator must inform the relevant clinical research associate (CRA, Monitor) by phone about the above mentioned events AND notify via email the sponsor within 24 hours of becoming aware of the event. Sponsor contact: Email safety@urogen.com with copies to sponsor@urogen.com.

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

In case event requires immediate reporting but the EDC system (eCRF) is not functioning, the site should use the relevant paper forms and email them to safety@urogen.com.

The investigator should report the event to the local/central IRB/national EC, according to local requirements.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to the sponsor. In the event of pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

19.2.3. Special Reporting Situations

Sponsor medicinal product that may require expedited reporting and/or safety evaluation include, but are not limited to:

1. Overdose of Investigational Product;
2. Suspected abuse/misuse of Investigational Product;
3. Inadvertent or accidental exposure to Investigational Product;
4. Medication error involving Investigational Product (with or without Patient/patient exposure to the sponsor medicinal product, e.g., name confusion).

19.2.4. Events of special interest

1. Allergic reaction to MMC severity grade 3 or 4 on the CTCAE Scale V 4.03 (Appendix VIII: CTACAE 4.03 Severity Grades, and Allergic Reaction Grades);
2. Urosepsis;
3. Ureteral events, including stenosis, as well as symptoms suspicious of ureteral perforation/rupture – (prolonged localized abdominal or flank pain, abdominal tenderness/acute abdomen);
4. Any unexpected adverse drug reaction with severity grade of 3 or 4 on the CTCAE Scale V 4.03 (Appendix VIII: CTACAE 4.03 Severity Grades, and Allergic Reaction GradesAppendix VIII);
5. Any level of urinary flow interruptions unrelated to enlarged prostate, e.g., Hesitancy , Interrupted urine stream, difficulty to urinate and urinary retention;
6. Onset of renal insufficiency or deterioration of renal function which occurred following treatment initiation;
7. Onset of hepatic insufficiency or deterioration of liver function which occurred following treatment initiation;
8. Any indication of bone marrow suppression:
   - Anemia: Acute decrease of HB of 2gr% and over or anemia severity grade 2 and over;
   - Neutropenia: New onset of Neutropenia grade 3 and over according to CTEAE version 4.0;
   - Leukopenia: Acute onset of leukopenia grade 3 and over according to CTEAE version 4.0;
   - Thrombocytopenia: Acute decrease of thrombocyte count to below 50,000/µL;
   - And any change in myeloid cellularity which in the opinion of the local PI indicates of possible health risk to the patient.
   - Any of these Events of Special Interest that also meet criteria of Serious Adverse Event should be reported as such.

19.2.5. Management of Anomalies in Laboratory Parameters

The investigator must review the patient's lab results and evaluate all anomalous laboratory values as clinically significant or not. Clinically significant results must be recorded as adverse events in the relevant section of the eCRF.

19.2.6. Progression of Underlying Malignancy Disease:

Progression of underlying malignancy should not be reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under trial.

19.2.7. Concomitant Illnesses and Pre-existing Conditions

Ongoing medical conditions and past cancer history other than urothelial carcinoma, and significant medical history up to 5 years back from screening must be collected and recorded in the eCRF.

Concomitant illnesses (including signs/symptoms of a pre-existing pathological condition) that are present during or before the administration of a product under trial and which are manifested with the same severity, frequency, or duration after administration of the medicinal product under trial must be recorded in the relevant section of the eCRF. However, cases which show an increase in the severity or duration of the concomitant illness or pre-existing condition must be reported as AEs.

19.2.8. Adverse Events Reporting Period

- The investigator is required to collect AEs beginning with informed consent signature. This information is to be entered into the eCRF.
- All serious adverse events, and All AEs which are suspected to be related to the study treatment and/or procedures occurring during the trial period should be reported throughout a subject's participation in the trial.
- Adverse events will be collected up to 30 days post last instillation or until resolution, and will be documented in the eCRF.
- In case of non-complete response patients - All adverse events should be recorded up to the PDE Visit or until resolution (5 weeks after the last instillation).
- **Progression of urothelial carcinoma disease should not be reported as an AE/SAE.**
- Death due to any cause occurring during the trial period including follow up period will be reported.
- Pregnancy should be reported at any time during the trial and during 6 months following last instillation (if site became aware of the pregnancy).

The investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this trial. The investigator should notify the trial sponsor of any death or any IP related adverse event.

19.2.9. Management of Adverse Events at Trial Conclusion

All unresolved adverse events should be followed by the investigator until the events are resolved, the patient is lost to follow-up, or the adverse event is otherwise explained.

Unresolved IP/Procedure Related Adverse Event

All IP-related AEs shall be monitored until resolution and/or diagnosis or otherwise explained. Where a related adverse event is not resolved upon conclusion of the trial, the investigator will evaluate the need to continue follow-up. All medicinal products taken during the trial to treat AEs or previous diagnoses must be recorded in the eCRF.

Unresolved Serious Adverse Events

SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

1. The event resolves;
2. The event stabilizes;
3. The event returns to baseline, if a baseline value/status is available;
4. It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts).

19.3. Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be appointed by the Sponsor

The DMC will be responsible for safeguarding the interests of the patients by assessing the safety of the intervention during the trial, and for reviewing the overall conduct of the clinical trial.

In addition, the DMC will have the responsibility to assess the efficacy data of the interim futility analysis and decide if stopping rules are met (see interim futility analysis in section 18). The DMC will have access to the individual treatment - and will be able to merge these with the collected trial data while the trial is ongoing.

Any unexpected AE related to MitoGel™ and qualified per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE; Appendix VIII: CTACAE 4.03 Severity Grades, and Allergic Reaction Grades) as grade 3 or 4 will be evaluated by the sponsor medical team and steering committee. In case of need, a DMC meeting will be gathered.

The DMC charter is prepared to detail precise roles and responsibilities, meetings timelines and procedures and criteria for considering study discontinuation.

20. Concomitant Medications

The site should collect information and record in the eCRF all ongoing therapies, all past cancer therapies (including procedures), and other significant therapies taken within one month prior to screening.

Concomitant medications given to treat an adverse event must be recorded in the eCRF.

Concomitant medications must be recorded in the relevant section of the clinical data sheet and the CRF. Refer to inclusion/exclusion criteria regarding excluded concomitant medication such as systemic chemotherapy, intravesical chemotherapy, and immunotherapy for cancer treatment including but not limited to BCG.

21. Ethical Considerations and Confidentiality

The trial will be performed in accordance with Food and Drug Administration (FDA) Good Clinical Practice (GCP) Regulations (Code of Federal Regulations [CFR] 21 parts 50, 56, and 312) and International Conference on Harmonization (ICH) GCP Guidelines (E6) and clinical safety data management (E2A).

21.1. Informed Consent

A properly executed, written informed consent form (ICF), in compliance with 21 CFR Part 50, must be obtained from each patient prior to enrollment and initiating screening evaluations required by this protocol. A copy of the ICF planned for use will be reviewed by the sponsor (or designee) for acceptability and must be submitted by the Investigator, together with the protocol, to the appropriate IRB/EC for review and approval prior to the start of the trial. Consent forms must be in a language fully comprehensible to the prospective patient. The Investigator must provide the sponsor (or designee) with a copy of the IRB/EC letter approving the protocol and the ICF(s) before the trial drug supplies will be shipped and the trial can be initiated.

The written consent form must be revised if new information becomes available during the trial that may be relevant to the Patient. Any revision(s) must be submitted to the appropriate IRB/EC for review and approval in advance of use. It is the responsibility of the investigators or of any individuals appointed by them to obtain the informed consent of all patients, having given them sufficient information regarding the objectives, methods, expected benefits and foreseeable risks of the trial. The investigators or such appointed workers must also inform participants that they shall not undergo any damages whatsoever should they choose not to take part in or to withdraw from the trial.

21.2. Ethics Committee and Competent Authorities

The sponsor shall provide the designated EC and the Competent Authorities with the trial protocol and any other related documents issued to the patient (Patient Information and ICF). Approval must be obtained from both the EC and the Competent Authorities before undertaking any procedures related to the trial and must be documented through an official communication to the investigator. In the event that changes need to be made to the trial protocol during the course of the trial, the sponsor shall submit to the designated EC a request for amendment to the protocol, which must be approved following the procedures set forth in the regulations established by that EC.

The sponsor, according the law in force, will be responsible to report to the all the National Competent Authorities, where the investigation has commenced, any SAE related to the study drug, and any Investigational Product Failure that might lead to an SAE or new findings/updates in relation to those already reported. For the duration of the clinical trial, the trial sponsor shall submit to all the National Competent Authorities and to the relevant Ethics Committee(s) a list of serious adverse reactions observed over the course of the reporting period, and a report on the safety of the individuals involved in the clinical trial. This will be done once a year or sooner if required by local regulations.

Sponsor reporting to the EC and National Competent authorities should be done as follows:

21.2.1. Fatal or Life-Threatening Unexpected ADRs

Regulatory agencies should be notified (e.g., by telephone, facsimile transmission, or in writing) as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

21.2.2. All Other Serious, Unexpected ADRs

Serious, unexpected reactions (ADRs) that are not fatal or life threatening must be filed as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

21.2.3. Minimum Criteria for Reporting

Information for final description and evaluation of a case report may not be available within the required periods for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met:

1. An identifiable patient;
2. A suspect medicinal product;
3. An identifiable reporting source;
4. And an event or outcome that can be identified as serious and unexpected, and for which, in clinical investigation cases, there is a reasonable suspected causal relationship.

Follow-up information should be actively sought and submitted as it becomes available.

22. Quality Control and Quality Assurance:

22.1. Source Documentation

At a minimum, source documentation must be available for the following to confirm data collected in the CRF: Patient identification, eligibility, and trial identification; trial discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all AEs and follow-up of AEs; concomitant medication; drug receipt/dispensing/return records; trial IP administration information; and date of trial completion and reason for early discontinuation of trial IP or withdrawal from the trial, if applicable.

In addition, the author of an entry in the source documents should be identifiable.

At a minimum, the type and level of detail of source data available for a trial Patient should be consistent with that commonly recorded at the site as a basis for standard medical care. Specific details required as source data for the trial will be reviewed with the investigator before the trial and will be described in the monitoring guidelines (or other equivalent document).

22.2. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all source documents that support the data collected from each patient, as well as all trial documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all trial documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 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 investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the trial records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any trial documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this trial, the investigator must permit access to such reports.

22.3. Clinical Monitoring

The sponsor will perform on-site monitoring visits as frequently as necessary, depending of 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 subjects, to assure eligibility. The first post-initiation visit will be made as soon as possible (approximately two weeks) after enrollment has begun. At these visits, the monitor will compare the data entered into the CRF 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 CRF 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 CRF are consistent with the original source data. Findings from this review of CRFs 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. A separate clinical monitoring plan was put in place.

22.4. 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 subject, the investigator, or the study site staff. 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 managements 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 per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements.

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

22.5. Audit and Inspection

Representatives of the sponsor's clinical quality assurance department may visit the site at any time during or after completion of the trial to conduct an audit of the trial in compliance with regulatory guidelines and company policy. These audits will require access to all trial records, including source documents, for inspection and comparison with the CRFs. Patient privacy must, however, be respected. The investigator and staff are responsible for being present and available for consultation during routinely scheduled site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this trial in support of a regulatory submission. The investigator should immediately notify the sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

23. Trial Systems

23.1. Data Collection and Management Responsibilities

The web based electronic data capturing (EDC) system (named Target e*Studio) used for data collection in provided by Target Health Inc.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into Target e*Studio, a 21 CFR Part 11 compliant data capturing system.

The data system includes password protection and internal quality verification 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.

Passwords are personal and not to be shared.

Data management services will be provided by TechnoSTAT Ltd., Israel. Data management plan will be in place.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported according to ICH E6. The site PI will login to the EDC and sign the patients' electronic Case Report Forms (eCRFs) after the database lock has achieved, thus confirming its content.

Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant’s official electronic study record.

23.2. Procedures & Timelines for Data Capturing

1. Patient registration in the Target system: Once patient signs informed consent, the site should register the patient in the system by completing the "Registration" eCRF form. The next sequential screening number available at the site should be recorded, starting at 001. The format of the screening number is 2 digits of the site number which is auto populated, followed by 'S', and 3 digits entered manually. Example: **05 S 001** (Site 05 patient screening number 001).
2. Patient enrollment number is given automatically by the Target system.
   In order to obtain enrollment number the following forms in the 'Screening' visit must be completed first: Screening 'Visit date', Target Treatment Area Lesion Mapping' form, 'Target

Treatment Area Lesion Mapping Information' form, 'Patient Eligibility by Investigator" AND the 'Patient Eligibility by Sponsor" forms.

3. To enroll a patient "Enrolment" tab should be selected from menu, data completed and submitted. The enrollment number will appear automatically.
   The format of the enrollment number is 2 digits of the site number, followed by 'E', and 3 digits which represent the running number of enrolled patients across all sites. Example: **05 E 010** (site 05, patient enrollment number 010).
4. The minimum data required in the eCRF for patients considered screen failures are:
   - Registration - Informed consent
   - Demographics
   - Inclusion Criteria
   - Exclusion Criteria
   - Patient Eligibility by site investigator
   - Patient Eligibility by sponsor - This page will trigger the removal OR opening of the other forms in the screening visits and all other visits forms
5. The site investigator is responsible that the data from trial patients' visits will be recorded in eCRF no longer than 5 working days following the visit. Timelines may shorten during database clean-up and database lock period.
6. Adverse event related queries must be resolved within 5 working days as well.
7. Initial report on subject's death, SAEs, SUSARs, and events of clinical interest must be reported in the eCRF within 24 hours. Paper SAE /AE forms will be supplied to the site for completion in case of technical problem with the eCRF, not to delay the required immediate reporting.
8. Queries relevant to subject's death, SAEs, SUSARs, and events of clinical interest must be resolved within 24 hours.
9. In case of delay in data recording/query resolution, the sites will receive email reminders reminding that data is to be completed.
10. An Interim Analysis is planned when 20 patients have performed PDE visit, for which all data must be clean and up to date at the time of analysis.

CRF data entry guidelines will be provided to all sites.

23.3. Acknowledgment of MitoGel™ Kit Shipment Receipt

MitoGel™ Kit inventory will be managed via Target Health web-based system. MitoGel™ Kits shipments will be shipped to the authorized site pharmacist. The pharmacist will receive a unique user name and password and should login to the system in order to confirm the receipt of shipments. In case shipment was sent to the site but was not confirmed in the system, the specific kits belonging to this shipment would not appear in the site inventory and the MitoGel™ Kit belonging to this shipment will not be dispensed. Therefore, the pharmacist should confirm shipments in the system as soon as they are received.

23.4. AG MedNet System for Images Upload

The authorized site personnel will receive an email invitation with link to the website and will be requested to create account to the site. Personal username and password are required to access the AG MedNet website. The sites are required to upload URS/CTU/MRI/Pyelography images performed during the following visits:

- Screening
- PDE visit
- Follow up visits 1-4
- Any unscheduled visit in which imaging was performed to determine eligibility, primary endpoint and secondary endpoint.

The AG MedNet system is validated and in compliance with FDA requirements and has a feature enabling the removal of patient identifiers while uploading the images to the portal.

24. Trial Completion/Termination

24.1. Trial Completion

The trial is considered completed with the last visit for the last Patient participating in the trial. The final data from the investigational site will be sent to the sponsor (or designee) after completion of the final Patient visit at that site, in the period specified in the Clinical Trial Agreement.

24.2. Trial Termination

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

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

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

1. Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines;
2. Inadequate recruitment of patients by the investigator;
3. Discontinuation of further drug development.

25. Changes in the Conduct of the Trial:

25.1. Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the Patients, in which case the amendment must be promptly submitted to the IRB and relevant competent authority. Documentation of amendment approval by the investigator and IRB must be provided to the sponsor or its designee. When the change(s) involves only logistic or administrative aspects of the trial, the IRB (and IEC where required) only needs to be notified.

During the course of the trial, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative (see Contact Information page(s) provided separately). Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

26. Study Leadership

Steering committee and data monitoring committee (DMC) have been assigned for this trial. DMC charter was put in place.

The Steering Committee will govern the conduct of the study. In case need arises, Ad hoc DMC meetings will be initiated by the steering committee.

Every effort will be made to reach a consensus within the DMC and with the principal coordinating investigator. In case of disagreement on recommended modifications, the Steering Committee will make the final decision.

27. Administrative and Regulatory Details

27.1. Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

27.2. Ownership of Data

All data is the property of the sponsor.

27.3. Conflict of Interest Policy

The independence of this study from any actual or perceived influence 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 trial. The study leadership 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.

27.4. Final Report and Publication of the Results

Publication of the trial results in scientific literature is encouraged and the investigator shall be entitled, consistent with academic standards, to publish the results of the trial patient to the stipulations set forth in research contract. The sponsor reserves the right to review any paper written utilizing data generated from the trial prior to such paper's presentation or submission for publication purposes. At least 90 (ninety) days prior to submitting or presenting a manuscript or other materials relating to the trial to a publisher, reviewer, or any third party, the investigator shall provide the sponsor a copy of all such manuscripts and materials, and allow the sponsor ninety (90) days to review and comment. The investigator will give due consideration to the sponsor's comments and should get prior in written consent from the sponsor to the content of any such publication. The investigator further agrees to delay the publication for an additional 120 days, at the request of the sponsor, where the sponsor considers such delay necessary for the protection of its intellectual property rights.

a) If the trial is a part of a multi-center trial and the sponsor wishes to publicize a joint publication, which includes results of all sites, then the investigator shall not publicize the trial results before the first joint publication, unless such publication is not published within 12 months from the completion of the trial at the trial center.
b) The sponsor can use, directly or indirectly, the name of the trial center and/or the investigator and/or any of the trial staff, in the sponsor's commercial publications.
c) The sponsor undertakes that should it publicize the results of the trial, it shall publish the results in full and avoid quoting matters out of context.

27.5. Finance and Insurance

27.5.1. Finance:

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

27.5.2. Insurance:

The trial will be covered in accordance to 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 investigational product or the participation in this trial the sponsor will contract the insurance company which 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.

28. Bibliography:

Aboumarzouk OM, Somani B, Ahmad S, Nabi G, Townell N, Kata SG. Mitomycin C instillation following ureterorenoscopic laser ablation of upper urinary tract carcinoma. Urol Ann. 2013 Jul;5(3):184-9. doi: 10.4103/0974-7796.115746.

Accord Healthcare Inc. Mitomycin for Injection (ANDA 064144) Label. 2011 .

Au JL, Badalament RA, Wientjes MG, Young DC, Warner JA, Venema PL et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst 2001; 93(8):597-604.

Au JL, Jang SH, Wientjes MG. Clinical aspects of drug delivery to tumors. J Control Release. 2002 Jan 17;78(1-3):81-95.

Audenet F, Traxer O, Bensalah K, Rouprêt M. Upper urinary tract instillations in the treatment of urothelial carcinomas: a review of technical constraints and outcomes. World J Urol. 2013a Feb;31(1):45-52. doi: 10.1007/s00345-012-0949-3.

Audenet F, Yates DR, Cussenot O, Rouprêt M. he role of chemotherapy in the treatment of urothelial cell carcinoma of the upper urinary tract (UUT-UUC). Urol Oncol. 2013b May;31(4):407-13. doi: 10.1016/j.urolonc.2010.07.016.

Barlogie B, Drewinko B. Lethal and cytokinetic effects of mitomycin C on cultured human colon cancer cells. Cancer Res. 1980 Jun;40(6):1973-80.

Bristol Laboratories DoB-MC. Mutamycin (Mitomycin for Injection, USP) Approved Label NDA 050450. 1985 .

Bristol-Meyers Squibb Company. Mutamycin-mitomycin for injection approved label ANDA 062336. 2004 .

Browne RF, Meehan CP, Colville J, Power R, Torreggiani WC. Transitional cell carcinoma of the upper urinary tract: spectrum of imaging findings. Radiographics. 2005 Nov-Dec;25(6):1609-27.

Colin P, Rouprêt M, Ghoneim TP, Traxer O, Zerbib M, Xylinas E. Conservative management of upper tract urothelial carcinoma in France: a 2004-2011 national practice report. Eur Urol. 2013 Feb;63(2):405-6. doi: 10.1016/j.eururo.2012.10.020.

Cutress ML, Stewart GD, Zakikhani P, Phipps S, Thomas BG, Tolley DA. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. BJU Int. 2012 Sep;110(5):614-28. doi: 10.1111/j.1464-410X.2012.11068.x.

De Bruijn EA, Sleeboom HP, van Helsdingen PJ, van Oosterom AT, Tjaden UR, Maes RA. Pharmacodynamics and pharmacokinetics of intravesical mitomycin C upon different dwelling times. Int J Cancer. 1992 May 28;51(3):359-64.

Deb AA, Wilson SS, Rove KO, Kumar B, Koul S, Lim DD, Meacham RB, Koul HK. Potentiation of mitomycin C tumoricidal activity for transitional cell carcinoma by histone deacetylase inhibitors in vitro. J Urol. 2011 Dec;186(6):2426-33. doi: 10.1016/j.juro.2011.07.107.

Eastham JA, Huffman JL. Technique of mitomycin C instillation in the treatment of upper urinary tract urothelial tumors. J Urol. 1993 Aug;150(2 Pt 1):324-5.

Elliott DS, Blute ML, Patterson DE, Bergstralh EJ, Segura JW. Long-term follow-up of endoscopically treated upper urinary tract transitional cell carcinoma. Urology. 1996 Jun;47(6): 819–25.

European Commission. European Commission Guide to Good Manufacturing Practice, Revision to Annex 1. 2003.

Grasso M, Fishman AI, Cohen J, Alexander B. Ureteroscopic and extirpative treatment of upper urinary tract urothelial carcinoma: a 15-year comprehensive review of 160 consecutive patients. BJU Int. 2012 Dec;110(11):1618-26. doi: 10.1111/j.1464-410X.2012.11066.x.

Grossfeld GD, Litwin MS, Wolf JS, Hricak H, Shuler CL, Agerter DC, Carroll PR. Evaluation of asymptomatic microscopic hematuria in adults: the American Urological Association best practice policy--part I: definition, detection, prevalence, and etiology. Urology. 2001 Apr;57(4):599-603.

Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees. Food and Drug Administration. March 2006. Retrieved 2015-03-24.

Hall MC, Womack S, Sagalowsky AI, Carmody T, Erickstad MD, Roehrborn CG. Prognostic factors, recurrence, and survival in transitional cell carcinoma of the upper urinary tract: a 30-year experience in 252 patients. Urology. 1998 Oct;52(4):594-601.

Hellenthal NJ, Shariat SF, Margulis V, Karakiewicz PI, Roscigno M, Bolenz C, Remzi M, Weizer A, Zigeuner R, Bensalah K, Ng CK, Raman JD, Kikuchi E, Montorsi F, Oya M, Wood CG, Fernandez

M. Adjuvant chemotherapy for high risk upper tract urothelial carcinoma: results from the Upper Tract Urothelial Carcinoma Collaboration. J Urol. 2009 Sep;182(3):900-6. doi: 10.1016/j.juro.

Hurwitz M, Spiess PE, Garcia JA, Pisters LL. Urothelial and Kidney Cancers. Cancer Management. 2011 Mar 25.

Jarrard DF, Potretzke AM, Downs T. Urothelial Tumors of the Renal Pelvis and Ureters: Treatment and Management. Medscape, Retrieved 2015-03-26.

Kalaitzis C, Zisimopoulos A, Giannakopoulos S, Touloupidis S. Ureteroscopic laser treatment of upper urinary tract urothelial cell carcinomas: can a tumour free status be achieved? Adv Urol. 2013;2013:429585. doi: 10.1155/2013/429585.

Kapoor A, Allard CB, Black P, Kassouf W, Morash C, Rendon R. Canadian guidelines for postoperative surveillance of upper urinary tract urothelial carcinoma. Can Urol Assoc J. 2013 Sep-Oct;7(9-10):306-11. doi: 10.5489/cuaj.1578.

Keeley FX Jr, Bagley DH. Adjuvant mitomycin C following endoscopic treatment of upper tract transitional cell carcinoma. J Urol. 1997 Dec;158(6):2074-7.

Kim TS, Oh JH, Rhew HY. The efficacy of adjuvant chemotherapy for locally advanced upper tract urothelial cell carcinoma. J Cancer. 2013 Oct 5;4(8):686-90. doi: 10.7150/jca.7326.

Krambeck AE, Thompson RH, Lohse CM, Patterson DE, Elliott DS, Blute ML. Imperative indications for conservative management of upper tract transitional cell carcinoma. J Urol. 2007 Sep;178(3 Pt 1):792-6; discussion 796-7.

Lughezzani G, Sun M, Perrotte P, Shariat SF, Jeldres C, Budäus L, Latour M, Widmer H, Duclos A, Bénard F, McCormack M, Montorsi F, Karakiewicz PI. Gender-related differences in patients with stage I and III upper tract urothelial carcinoma: results from the Surveillance, Epidemiology, and End Results database. Urology. 2010 Feb;75(2):321-7. doi: 10.1016/j.urology.2009.09.048.

Martínez-Piñeiro JA, García Matres MJ, Martínez-Piñeiro L. Endourological treatment of upper tract urothelial carcinomas: analysis of a series of 59 tumors. J Urol. 1996 Aug;156(2 Pt 1):377-85.

Matin SF, Margulis V, Kamat A, Wood CG, Grossman HB, Brown GA, Dinney CP, Millikan R, Siefker-Radtke AO. Incidence of Downstaging and Complete Remission After Neoadjuvant Chemotherapy for High-Risk Upper Tract Transitional Cell Carcinoma. Cancer. 2010 Jul

1;116(13):3127-34. doi: 10.1002/cncr.25050.?Medical Enterprises Group. Synergo SB-TS 101.1 Device: Patient Information Guide. 2008 .

Messer JC, Terrell JD, Herman MP, Ng CK, Scherr DS, Scoll B, Boorjian SA, Uzzo RG, Wille M, Eggener SE, Lucas SM, Lotan Y, Shariat SF, Raman JD. Multi-institutional validation of the ability of preoperative hydronephrosis to predict advanced pathologic tumor stage in upper-tract urothelial carcinoma. Urol Oncol. 2013 Aug;31(6):904-8. doi: 10.1016/j.urolonc.2011.07.011.

Mohamed A, Elkoushy PD. Andonian VS. percutaneous instillation of chemolytic, chemotherapeutic, and antifungal agents.Smith's Textbook of Endourology, edited by Glenn Preminger, Gopal Badlani, Louis Kavoussi John Wiley & Sons, Nov 29, 2011 - Chapter 26: 290-303

Martinez-Pineiro JA, Garcia Matres MJ, Martinez-Pineiro L. Endourological Treatment of Upper Tract Urothelial Carcinomas: Analysis of a Series of 59 Tumors. J Urol. 1996 Aug;156(2): 377–85.

National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0, NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Bladder Cancer. Version 1.2014. 2013 .

Nepple KG, Joudi FN, O'Donnell MA. Review of topical treatment of upper tract urothelial carcinoma. Adv Urol. 2009:472831. doi: 10.1155/2009/472831.

Nozue M, Todoroki T, Fukao K. 5-fu dose-dependency in mtx/s-fu sequential therapy assessed by in-vitro assay using gastric-cancer cell-lines. Oncol Rep. 1995 Sep;2(5):737-40.

O'Malley R, Kaag M, O'Malley P, Godoy G, Chen ML, Smaldone MC, Hrebinko RL, Vora KC, Bochner BH, Dalbagni G, Stifelman MD, Taneja SM, Huang WC, et al. Do changes in renal function following nephroureterectomy impact the use of perioperative chemotherapy? J Urol. 2009;181(4)(Suppl):136. doi: 10.1016/S0022-5347(09)60393-1

O'Brien T, Ray E, Singh R, Coker B, Beard R; British Association of Urological Surgeons Section of Oncology. Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol. 2011 Oct;60(4):703-10. doi: 10.1016/j.eururo.2011.05.064.

O'Donoghue JP, Crew JP. Adjuvant topical treatment of upper urinary tract urothelial tumours. BJU Int. 2004 Sep;94(4):483-5.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982

Ozawa S, Sugiyama Y, Mitsuhashi Y, Kobayashi T, Inaba M. Cell killing action of cell cycle phase-non-specific antitumor agents is dependent on concentration--time product. Cancer Chemother Pharmacol 1988; 21(3):185-190

Pak RW, Moskowitz EJ, Bagley DH. What is the cost of maintaining a kidney in upper-tract transitional-cell carcinoma? An objective analysis of cost and survival. J Endourol. 2009 Mar;23(3):341-6. doi: 10.1089/end.2008.0251.

Park BH, Jeon SS. Endoscopic management of upper urinary tract urothelial carcinoma. Korean J Urol. 2013 Jul;54(7):426-32. doi: 10.4111/kju.2013.54.7.426.

Perry RR, Greaves BR, Rasberry U, Barranco SC. Effect of treatment duration and glutathione depletion on mitomycin C cytotoxicity in vitro. Cancer Res. 1992 Sep 1;52(17):4608-12.

Porten S, Siefker-Radtke AO, Xiao L, Margulis V, Kamat AM, Wood CG, Jonasch E, Dinney CP, Matin SF. Neoadjuvant chemotherapy improves survival of patients with upper tract urothelial carcinoma. Cancer. 2014 Jun 15;120(12):1794-9. doi: 10.1002/cncr.28655.

Ristau BT, Tomaszewski JJ, Ost MC. Upper tract urothelial carcinoma: current treatment and outcomes. Urology. 2012 Apr;79(4):749-56.

Rouprêt M, Babjuk M, Compérat E, Zigeuner R, Sylvester R, Burger M, Cowan N, Böhle A, Van Rhijn BW, Kaasinen E, Palou J, Shariat SF; European Association of Urology. European guidelines on upper tract urothelial carcinomas: 2013 update. Eur Urol. 2013 Jun;63(6):1059-71. doi: 10.1016/j.eururo.2013.03.032.

Rouprêt M, Colin P, Yates DR. A new proposal to risk stratify urothelial carcinomas of the upper urinary tract (UTUCs) in a predefinitive treatment setting: low-risk versus high-risk UTUCs. Eur Urol. 2014 Aug;66(2):181-3. doi: 10.1016/j.eururo.2013.12.007.

Rouprêt M, Hupertan V, Sanderson KM, Harmon JD, Cathelineau X, Barret E, Vallancien G, Rozet F. Oncologic control after open or laparoscopic nephroureterectomy for upper urinary tract transitional cell carcinoma: a single center experience. Urology. 2007 Apr;69(4):656-61.

Rouprêt M, Zigeuner R, Palou J, Boehle A, Kaasinen E, Sylvester R, Babjuk M, Oosterlinck W. European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. Eur Urol. 2011 Apr;59(4):584-94. doi: 10.1016/j.eururo.2010.12.042.

Sadeghi HM, Seitz B, Hayashi S, LaBree L, McDonnell PJ. In vitro effects of mitomycin-C on human keratocytes. J Refract Surg. 1998 Sep-Oct;14(5):534-40.

Sakamoto N1, Naito S, Kumazawa J, Ariyoshi A, Osada Y, Omoto T, Fujisawa Y, Morita I, Yamashita H; Kyushu University Urological Oncology Group. Prophylactic intravesical instillation of mitomycin C and cytosine arabinoside for prevention of recurrent bladder tumors following surgery for upper urinary tract tumors: a prospective randomized study. Int J Urol. 2001 May;8(5):212-6.

Schmittgen TD, Wientjes MG, Badalament RA, Au JL. Pharmacodynamics of mitomycin C in cultured human bladder tumors. Cancer Res. 1991 Aug 1;51(15):3849-56.

Scolieri MJ, Paik ML, Brown SL, Resnick MI. Limitations of computed tomography in the preoperative staging of upper tract urothelial carcinoma. Urology. 2000 Dec 20;56(6):930-4.

Singh P, Kumar R. Endourology for Upper Tract Lesions. JIMSA. 2011 Jul-Sep:24(3): 127-130.

Slee PH, de Bruijn EA, Leeflang P, Kuppen PJ, van den Berg L, van Oosterom AT. Variations in exposure to mitomycin C in an in vitro colony-forming assay. Br J Cancer. 1986 Dec;54(6):951-5.

Smith AK, Stephenson AJ, Lane BR, Larson BT, Thomas AA, Gong MC, Jones JS, Campbell SC, Hansel DE. Inadequacy of biopsy for diagnosis of upper tract urothelial carcinoma: implications for conservative management. Urology. 2011 Jul;78(1):82-6. doi: 10.1016/j.urology.2011.02.038.

Sverrisson EF, Kim T, Espiritu PN, Sexton WJ, Pow-Sang JM, Dhillon J, Spiess PE. The merits of cytology in the workup for upper tract urothelial carcinoma - a contemporary review of a perplexing issue. Int Braz J Urol. 2014 Jul-Aug;40(4):493-8. doi: doi: 10.1590/S1677-5538.IBJU.2014.04.07.

Tavora F, Fajardo DA, Lee TK, Lotan T, Miller JS, Miyamoto H, Epstein JI. Small endoscopic biopsies of the ureter and renal pelvis: pathologic pitfalls. Am J Surg Pathol. 2009 Oct;33(10):1540-6. doi: 10.1097/PAS.0b013e3181aec42a.

TheraCoat Report No. TAS-4M-P-A-133 Revision 3, Mitomycin C Concentrations in Urothelial Tissue Following Intravesical Instillation of TC-3 + Mitomycin C in Pigs. 3-17-2014a .

Volanis D, DashGupta R, Patel A. Endoscopic Nephron-sparing Management of Superficial LG UTUC. Eur Urol Rev . 2012; 7(1) 10-14 .

Walker MC, Masters JR, Parris CN, Hepburn PJ, English PJ. Intravesical chemotherapy: in vitro studies on the relationship between dose and cytotoxicity. Urol Res. 1986;14(3):137-40.

Wang AJ, Goldsmith ZG, Neisius A, Astroza GM, Oredein-McCoy O, Iqbal MW, Simmons WN, Madden JF, Preminger GM, Inman BA, Lipkin ME, Ferrandino MN. Increasing dwell time of mitomycin C in the upper tract with a reverse thermosensitive polymer. J Endourol. 2013 Mar;27(3):288-93. doi: 10.1089/end.2012.0211.

WHO Classification: Eble JN, Sauter G, Epstein JI and Sesterhenn IA: World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Urinary and Male Genital Organs. Lyon: IARCPress 2004.

Yoshimura K, Utsunomiya N, Ichioka K, Matsui Y, Terai A, Arai Y. Impact of superficial bladder cancer and transurethral resection on general health-related quality of life: an SF-36 survey. Urology. 2005 Feb;65(2):290-4.

Wewers ME, Lowe NK. A Critical Review of Visual Analogue Scales in the Measurement of Clinical Phenomena Research in Nursing & Health, 1990, 13, 227-236.

Appendix I: Clinical Evaluation

General physical Examination (V0, V9) General Appearance Cardiovascular system Respiratory HEENT (head, eyes, ears, nose & throat) and neck Abdomen Extremities Neurologic Skin Other *specify*: _____
Urology Oriented Examination (V0-V6) Urethral meatus Perineal skin and mucous membranes Scrotum and Testes (for male patients) Lymphadenopathy Palmar erythema Rectal Examination - Prostate (for male patients; Screening visit only)

Appendix II: Vital Signs

- Blood Pressure
- Heart Rate
- Body Temperature
- Weight (only at screening)
- Height (only at screening)

Appendix III: Required Lab Tests

The samples' handling, packaging, and shipping details will be given in the site and central lab manual.

<table>
<tr>
<td><u>Liver Function Tests</u> *
• SGOT/AST
• SGPT/ALT
• GGT
• Alkaline phosphatase
• Total Bilirubin
• Direct Bilirubin
• Albumin
• Total Protein</td>
<td><u>Renal Function Tests</u>
• Creatinine
• BUN or Urea Nitrogen
• Uric acid
• Sodium
• Potassium
• Phosphorus
• Calcium</td>
</tr>
<tr>
<td><u>Hematology Tests</u> *
• Complete blood count, including red blood cell indices and white blood cell differential
• Platelet count</td>
<td><u>Coagulation Tests</u>
• Prothrombin Time (PT)
• INR</td>
</tr>
<tr>
<td><u>Pregnancy Test</u> **
• Serum
• Urine dip stick for pregnancy</td>
<td rowspan="4"><u>Urinalysis</u>
• Specific gravity
• pH
• Glucose
• Urogilinogen
• Bilirubin
• Blood
• Protein
• Nitrites Leukocyte Esterase
• Microscopic examination
• Bacteriuria (if required)
• WBC</td>
</tr>
<tr>
<td><u>Urine Culture (at screening), on all other visits only if urinalysis if suspicious for UTI</u></td>
</tr>
<tr>
<td><u>Urine Cytology</u>***
<u>Upper Tract washing Urine Cytology</u></td>
</tr>
<tr>
<td><u>Histology</u>***</td>
</tr>
<tr>
<td><u>MMC Levels</u> <u>(6 Patients)</u>****
Serum</td>
<td></td>
</tr>
</table>

* The amount of blood required for hematology and biochemistry tests per visit is 15–20 cc.

** The amount of blood required for pregnancy tests per visit is 5 cc.

Women of non-childbearing potential are defined as:

a. At least 12 months since the last menstrual bleeding, or
b. Without uterus and/or both ovaries, or
c. Has been surgically sterile for at least 6 months prior to trial drug administration.

*** Biopsy slides and urine cytology samples/slides will be sent to the central lab for central reading-a manual will be provided in separate to the pathology lab.

**** 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. Refer to **Appendix VII.**

Appendix IV: Questions 24–32 hours Post Treatment Visit

TC-UT-03-P Trial UroGen Pharma

Instillations no. 1-6

Telephone Contact 24-32 Hours after Instillation

Site no. _____ Patient Enrollment no. _____ -_____

*Relevant only to patients who receive treatment via retrograde catheterization

1. Date of phone contact:
   Date ☐☐-☐☐☐-☐☐☐☐
   DD Mon YYYY

2. Time of phone contact: ☐☐ : ☐☐
   HH : MM

3. How long after the treatment did you have your first urination?
   ☐☐.☐ Hours

4. How long after the treatment was the urine clear (no purple color) for the first time?

   ☐☐☐.☐ Hours

Call made by (Name)_____

Study role: (Nurse/study coordinator/investigator)_____

TC-UT-03-P Version 1 dated 13/Aug/16 -Telephone Contact Questions

Confidential

Appendix V: Karnofsky & ECOG Scores (Oken et al, 1982)

Performance Scales: Karnofsky & ECOG Scores

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death no imminent	30	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Dead	0	5	Dead

Appendix VI: Recommended Antimicrobial Prophylaxis for Urologic Procedure

Taken from "Best Practice Statement on urologic surgery antimicrobial prophylaxis"

Table 3a. Recommended antimicrobial prophylaxis for urologic procedures

Procedure	Organisms	Prophylaxis Indicated	Antimicrobial(s) of Choice	Alternative Antimicrobial(s)	Duration of Therapy*
Lower Tract Instrumentation					
Removal of external urinary catheter	GU tract†	If risk factors‡,§	- Fluoroquinolone¶‖ - TMP-SMX¶	- Aminoglycoside (Aztreonam¥) ± Ampicillin¶ - 1st/2nd gen. Cephalosporin¶ - Amoxacillin/Clavulanate¶	≤24 hours¶
Cystography, urodynamic study, or simple cystourethroscopy	GU tract	If risk factors§	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (Aztreonam¥) ± Ampicillin - 1st/2nd gen. Cephalosporin - Amoxacillin/Clavulanate	≤24 hours
Cystourethroscopy with manipulation ‖	GU tract	All	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (Aztreonam¥) ± Ampicillin - 1st/2nd gen. Cephalosporin - Amoxacillin/Clavulanate	≤24 hours
Prostate brachytherapy or cryotherapy	Skin	Uncertain	- 1st gen. Cephalosporin	- Clindamycin**	≤24 hours
Transrectal prostate biopsy	Intestine††	All	- Fluoroquinolone - 1st/2nd/3rd gen. Cephalosporin	- TMP-SMX - Aminoglycoside (Aztreonam¥)	≤24 hours
Upper Tract Instrumentation					
Shock-wave lithotripsy	GU tract	If risk factors	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (Aztreonam¥) ± Ampicillin - 1st/2nd gen. Cephalosporin - Amoxacillin/Clavulanate	≤24 hours
Percutaneous renal surgery	GU tract and skin‡‡	All	- 1st/2nd gen. Cephalosporin - Aminoglycoside (Aztreonam¥) + Metronidazole or Clindamycin	- Ampicillin/Sulbactam - Fluoroquinolone	≤24 hours
Ureteroscopy	GU Tract	All	- Fluoroquinolone - TMP-SMX	- Aminoglycoside (Aztreonam¥) ± Ampicillin - 1st/2nd gen. Cephalosporin - Amoxacillin/Clavulanate	≤24 hours
Open or Laparoscopic Surgery					
Vaginal surgery (includes urethral sling procedures)	GU tract, skin and Grp B *Strep.*	All	- 1st/2nd gen. Cephalosporin - Aminoglycoside (Aztreonam¥) + Metronidazole or Clindamycin	- Ampicillin/Sulbactam - Fluoroquinolone	≤24 hours
Without entering urinary tract	Skin	If risk factors	- 1st gen. Cephalosporin	- Clindamycin	Single dose
Involving entry into urinary tract	GU tract and skin	All	- 1st/2nd gen. Cephalosporin - Aminoglycoside (Aztreonam¥) + Metronidazole or Clindamycin	- Ampicillin/Sulbactam - Fluoroquinolone	≤24 hours
Involving intestine §§	GU tract, skin and intestine	All	- 2nd/3rd gen. Cephalosporin - Aminoglycoside (Aztreonam¥) + Metronidazole or Clindamycin	- Ampicillin/Sulbactam - Ticarcillin/Clavulanate - Pipercillin/Tazobactam - Fluoroquinolone	≤24 hours
Involving implanted prosthesis	GU tract and skin	All	- Aminoglycoside (Aztreonam¥) + 1st/2nd gen. Cephalosporin or Vancomycin	- Ampicillin/Sulbactam - Ticarcillin/Clavulanate - Pipercillin/Tazobactam	≤24 hours

Order of agents in each column is not indicative of preference. The absence of an agent does not preclude its appropriate use depending on specific situations.

Key

* Additional antimicrobial therapy may be recommended at the time of removal of an externalized urinary catheter.

† GU tract: Common urinary tract organisms are *E. coli, Proteus sp., Klebsiella sp., Enterococcus.*

‡ See Table 1 "Patient-related factors affecting host response to surgical infections."

§ If urine culture shows no growth prior to the procedure, antimicrobial prophylaxis is not necessary.

¶ Or full course of culture-directed antimicrobials for documented infection (which is treatment, not prophylaxis).

¥ Aztreonam can be substituted for aminoglycosides in patients with renal insufficiency.

‖ Includes transurethral resection of bladder tumor and prostate, and any biopsy, resection, fulguration, foreign body removal, urethral dilation or urethrotomy, or ureteral instrumentation including catheterization or stent placement/removal.

**Clindamycin, or aminoglycoside + metronidazole or clindamycin, are general alternatives to penicillins and cephalosporins in patients with penicillin allergy, even when not specifically listed.

†† Intestine: Common intestinal organisms are *E. coli, Klebsiella sp., Enterobacter, Serratia sp, Serratia sp., Proteus sp., Enterococcus*, and Anaerobes.

‡‡ Skin: Common skin organisms are *S. aureus*, coagulase negative *Staph. sp.*, Group A *Strep. sp.*

§§ For surgery involving the colon, bowel preparation with oral neomycin plus either erythromycin base or metronidazole can be added to or substituted for systemic agents.

Key: gen, generation; GU, genitourinary; TMP-SMX, trimethoprim-sulfamethoxazole

Copyright © 2007 American Urological Association Education and Research, Inc.® *28*

Updated September 2008

Revised 9/20/2012Copyright

Appendix VII: Collection and Handling of Plasma Samples for MMC Pharmacokinetics

Plasma MMC levels will be analyzed at AIT Bioscience Lab.

Address: 7840 Innovation Blvd, Indianapolis, IN 46278, USA

Instructions for plasma collection and handling are as follows:

CAUTION! HANDLING OF THE SAMPLES SHOULD BE DONE WITH CAUTION ACCORDING TO THE INSTITUTE GUIDELINES FOR HANDLING CYTOTOXIC SAMPLES

1. Time points of plasma PK sampling: Time 0 (prior to instillation), 30min, 1, 2, 3, 4, 5 and 6 hr post instillation. For the sampling of 30 min. post treatment the deviation is ±5 minute. For sampling of 1-6 hours post treatment, allowed window is ±9 minutes.

2. ***Attention! Mitomycin C is sensitive to light!!***
   At each time point collect 3mL of blood into K2EDTA tube (supplied by UroGen) and place immediately in Ice (2-8°C) inside a closed cooling box protected from light. If the cooling box is unprotected from light, make sure to cover the collecting tubes with aluminum foil immediately after collection and then place them in ice.

3. Centrifuge the tubes immediately after collection. If this not possible, maintain the tubes prior to centrifugation in ice (2-8^{0}C) for no longer than 1 hour

4. Use refrigerated centrifuge for plasma separation. Centrifuge at 3000 RPM for 10 min.

5. Transfer the plasma from each collecting tube using a disposable plastic pipette into 2 X 2mL Eppendorf tubes (one will be shipped later to AIT central lab, the second will be left at the site as a backup)

6. Place the samples in a box protected from light (supplied by UroGen)

7. Immediately store the box in -70^{0}C deep freeze.

8. The shipping of the samples to AIT central lab will be done in coordination with the CRA.

Labeling of Plasma Collecting Tubes and Eppendorf Tubes

Prior to each blood collection verify you have collecting tube and matching Eppendorf tubes of the required time point. *Plasma labels Example:*

Pre dose

TC-UT-03 **Plasma** MMC

Pre-dose Time: __ : __

Site / Pt. Number: __/__

Date: __/___/__

Post dose, time 0.5 hour

TC-UT-03 **Plasma** MMC

PK: 0.5 h Time: __ : __

Site / Pt. Number: __/__

Date: __/___/__

Appendix VIII: CTACAE 4.03 Severity Grades, and Allergic Reaction Grades

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

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

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

Activities of Daily Living (ADL)

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Immune system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					

Source:

(http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)

Appendix IX: Protocol Amendment Version 6.0 – Summary of Changes

Note: Modified part is in **Bold** font

Section Updated	Protocol Version 5.0 Original Text	Protocol Version 6.0 Description of Change / New Text
Trial title	*A Phase 3 Multicenter Trial Evaluating the Efficacy and Safety of MitoGel™ on Ablation of Upper Urinary Tract Urothelial Carcinoma*	UGN-101 was added: A Phase 3 Multicenter Trial Evaluating the Efficacy and Safety of MitoGel™ (**UGN-101**) on Ablation of Upper Urinary Tract Urothelial Carcinoma
13.3.1. General Instructions for Instillation Visits	*"GFR ≥30"; "In the event that one or more of the above values are outside of the required limits, and the PI is confident that the treatment can be safely performed, he/she should contact UroGen Trial manager to obtain approval to proceed to treatment":*	Deleted: ~~In case of use of an external lab, the external lab's quality assurance documentation, normal ranges and CV of head lab must be collected by the site~~ Deleted: ~~*"GFR ≥30"*~~; "~~In the event that one or more of the above values are outside of the required limits, and the PI is confident that the treatment can be safely performed, he/she should contact UroGen Trial manager to obtain approval to proceed to treatment~~"; Added " • **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"; " o A repeated volumetric measurements may be performed prior to each instillation, at the discretion of the treating investigator";** • **For all other patients, changes in creatinine should not result in GFR less than 30mL/min/1.73m2.**
13.3.1 General Instructions for Instillation Visits	*If parameters do not conform to the detailed above, treatment will be postponed until recuperation for up to 4 weeks.*	Wording revised: If laboratory parameters do not conform to the detailed above, treatment will be postponed until laboratory values improve, for up to 4 weeks.
13.3.1 General Instructions for Instillation Visits		Added: Repeated volumetric measurements may be performed prior to each instillation, at the discretion of the treating investigator.
13.3.3. Instillation Procedure	*" For instillation, a 7–8 Fr ureter catheter supplied by UroGen shall be used."; "Prior to every instillation, the investigator must review the pyelocalyceal volume measurement done for that patient, withdraw the exact volume required into the syringe…"*	Added: " •For instillation, a 7–8 Fr ureter catheter supplied by UroGen shall be used. **in situations where it is technically challenging to pass the Urogen provided 7Fr catheter, a 5Fr Ureteral Catheter with molded Luer-Lock port may be used.**"; Prior to every instillation, the investigator must review the pyelocalyceal volume measurement done for that patient. **A repeated volumetric measurements may be performed prior to each instillation, at the discretion of the treating investigator. and The investigator must** withdraw the exact volume required into the syringe…"

Section Updated	Protocol Version 5.0 Original Text	Protocol Version 6.0 Description of Change / New Text
13.3.5. Instillations #2–#6 Visit Procedures (V2–V6)	*"CBC (complete blood count) - Should be performed in 1st week and 3rd week following the 6th instillation. This blood test can be performed also in the patient's local clinic. The CBC results should be recorded in the CRF."*	Updated: "CBC (complete blood count), **renal and liver blood function** ~~and coagulation~~ - Should be performed in 1st week and 3rd week following the 6th instillation. This blood test can be performed also in the patient's local clinic. The CBC, **renal and liver blood function** ~~and coagulation~~ results should be recorded in the CRF."
13.4 LAB 1 (V7) & LAB 2 (V8):	*" One week and 3 weeks following the last of the weekly instillations, complete blood count tests ..."*	Updated: " One week and 3 weeks following the last of the weekly instillations, **CBC (**complete blood count**), renal and liver blood function** ~~and coagulation~~ tests…"
13.9. Treatment Discontinuation	*Heading: "Treatment Discontinuation Visit"; " If a patient discontinues during the treatment period or at any time prior to the PDE Visit, an unscheduled visit should be done (one month after the last installation treatment) in which following activities should be performed:* *All assessments scheduled to be conducted during the PDE visit (Section 13.4);* *If the patient appears to have CR, document if the patient agrees to continue FU within the trial;"*	Updated: " **Treatment discontinuation prior to PDE** If a patient discontinues during the treatment period or at any time prior to the PDE Visit, ~~an unscheduled visit should be done (one month after the last installation treatment) in which~~ **the patient to complete PDE visit within 4+/-1 week of last instillation** ~~following activities should be performed:~~ **and perform all** ~~All~~ assessments ~~scheduled to be conducted during the~~**of the** PDE visit (Section 13.4); If the patient appears to have CR **at PDE**, ~~document if the patient agrees~~**patient should continue** ~~to continue~~ FU within the trial **receiving the maintenance treatments should be considered as well**;"; Sub-heading was added: "**Treatment Discontinuation during Maintenance**"
14. Schedule of Events 14.1. Part I - All Patients - Up to PDE Visit	CBC, liver and renal function, coagulation, wk 6 and wk 8 *: "Only CBC"*	Updated: "~~Only CBC~~ **X**" (X stand for CBC, liver and renal function, coagulation)
18. Statistical Methodology		Added: "**A formal Statistical Analysis Plan (SAP) will be developed and finalized prior to database lock. The SAP will supersede this statistical analysis section.**"
18.4.1. Safety Analysis Set	"...Intent-to-Treat (ITT) Analysis Set The intent to treat (ITT) analysis set will consist of all patients enrolled in the trial who have a confirmed diagnosis of LG UTUC by local pathology and have received at least one instillation of MitoGel™."; *" ITT subjects with no observed value on primary efficacy will be imputed primary efficacy failures. At the same time, sensitivity analyses will evaluate the robustness of results to different*	Updated: " Intent-to-Treat (ITT) Analysis Set **(=safety analysis set)**. ~~The intent to treat (ITT) analysis set will consist of all patients enrolled in the trial who have a confirmed diagnosis of LG UTUC by local pathology and have received at least one instillation of MitoGel™~~"; Updated: " ITT subjects with no observed value on primary efficacy will be imputed primary efficacy failures. **Note that this only include patients who dropped from the study for any reason before the PDE evaluation**. At the same time, sensitivity analyses will evaluate the robustness of results to different assumptions of missingness. ~~For the key secondary endpoint only observed data will be used.~~

Section Updated	Protocol Version 5.0 Original Text	Protocol Version 6.0 Description of Change / New Text
	assumptions of missingness. *For the key secondary endpoint only observed data will be used."*	**Treatment of missing values for the secondary endpoint detailed in Section 18.7.2**."
18.4.2. Local Modified Intent-to-Treat (mITT) Analysis Set	Heading:" 18.4.2. Modified Intent-to-Treat (mITT) Analysis Set"; " The modified intent to treat (mITT) analysis set will be a subset of ITT subjects with confirmed LG UTUC at Screening by central lab."	Added:" 18.4.2. **Local** Modified Intent-to-Treat (mITT) Analysis Set"; " The **local** modified intent to treat (local - mITT) analysis set will be a subset of ITT subjects with confirmed LG UTUC at Screening **by local lab and who arrived to the PDE evaluation**. ~~by central lab~~."
18.4.3. Central Modified Intent-to-Treat (mITT) Analysis Set		Section was added:" **The central modified intent to treat (Central - mITT) analysis set will be a subset of ITT subjects with confirmed LG UTUC at Screening by central lab and who arrived to the PDE evaluation and received the central lab diagnostic.** **Missing values: Only observed values will be used in central - mITT; i.e. missing data will not be imputed.**"
18.4.4. Per Protocol (PP) Analysis Set 1	*"18.4.3 Per Protocol (PP) Analysis Set 1";* *" The Per Protocol (PP) analysis set is a subset of the mITT Analysis Set…"*	Updated: "18.4.~~3~~**4** Per Protocol (PP) Analysis Set 1"; " The Per Protocol (PP) analysis set is a subset of the Local mITT Analysis Set…"
18.4.5. Per Protocol (PP) Analysis Set 1	*"18.4.4 Per Protocol (PP) Analysis Set 2";* *" The Per Protocol (PP) analysis set is a subset of the mITT Analysis Set…"*	Updated: "18.4.4**5** Per Protocol (PP) Analysis Set 2"; " The Per Protocol (PP) analysis set is a subset of the Local mITT Analysis Set…"
18.4.6. Complete Responders at the PDE Visit (PDE_{CR}) Analysis Set	*"18.4.5. Complete Responders at the PDE Visit (PDE_{CR}) Analysis Set"*	"18.4.~~5~~**6** Complete Responders at the PDE Visit (PDE_{CR}) Analysis Set"
18.7.2. Sensitivity Analysis for the Principal Analysis of the Primary Endpoint	*" The primary analysis described in the previous section will be repeated using* *o Only observed data from ITT (i.e., excluding missing data imputed "failure")* *o mITT population* *o PP1 population* *PP2 population"*	Updated: " The primary analysis described in the previous section will be repeated using **o Local diagnosis in Local-mITT, PP1, PP2 populations** **o Central diagnosis in Central-mITT** o ~~Only observed data from ITT (i.e., excluding missing data imputed "failure")~~ ~~o mITT population~~ ~~o PP1 population~~ ~~o PP2 population~~"
18.7.4. Sensitivity Analysis for the Dichotomous Key Secondary Endpoint		Section was added: " **For dichotomous key secondary analysis, patients who did not arrive the last FU visit and have no prior recurrence, are treated as Failures (which is the "worst case" imputation scenario). Sensitivity analysis will be done to examine the results if alternative imputation scenarios are**

Section Updated	Protocol Version 5.0 Original Text	Protocol Version 6.0 Description of Change / New Text
		used. Specifically, the tipping point imputation will be applied. **In this analysis we begin by imputing all missing subjects (early terminations) "Success" (or CR). Then, at each step, number of imputed "Successes" will reduce by one and number of imputed "Failures" will increase by 1, until the case where all missing values are imputed "Failure" (which is equivalent to the primary analysis). For each imputation scenario, exact binomial hypothesis testing p-value will be reported.** **In addition, to the described above, analysis where only observed data is used will be done**."
18.7.5. Secondary Efficacy Analyses	*"18.7.4. Secondary Efficacy Analyses"*	Updated: "18.7.4**5**.Secondary Efficacy Analyses"
19.1.4. Causality	*" • Non-classified/Non-Classifiable* *A clinical event for which there is insufficient information at the time of its discovery and for which additional data is required to perform an adequate evaluation. A clinical event for which the information received is inadequate and/or contradictory and is unable to provide for a reasonable ascertainment."*	Paragraph was deleted:" ~~• Non-classified/Non-Classifiable~~ ~~A clinical event for which there is insufficient information at the time of its discovery and for which additional data is required to perform an adequate evaluation. A clinical event for which the information received is inadequate and/or contradictory and is unable to provide for a reasonable ascertainment.~~"
19.2.2. Events Requiring Immediate (24 hours) Reporting	*" …3. Pregnancy and outcome of the pregnancy;* *4. Special reporting situation event / Event of clinical Interest* *5. Any of the event which requires treatment discontinuation (section 17.1.1)* *The investigator must inform the site clinical research associate (CRA, Monitor) by phone about the above mentioned events AND notify via email both site CRA and sponsor within 24 hours* *Initial SAE/Death/Pregnancy/Special or clinical interest events report must be recorded in the electronic Case Report Form (eCRF) within 24 hours of first knowledge of the event.* *In case event requires immediate reporting but the EDC system (eCRF) is not functioning, the site should use the relevant paper forms and fax to the sponsor within 24 hours of site being made*	Updated:" …3. Pregnancy and outcome of the pregnancy; ~~4. Special reporting situation event / Event of clinical Interest~~ ~~5. Any of the event which requires treatment discontinuation (section 17.1.1)~~ The investigator must inform the ~~site~~ **relevant** clinical research associate (CRA, Monitor) by phone about the above mentioned events AND notify via email ~~both site CRA and~~**the** sponsor within 24 hours **of becoming aware of the event. after its occurrence first came to his knowledge. Sponsor contact: Email safety@urogen.com with copies to sponsor@urogen.com.** Initial SAE/Death/Pregnancy~~/Special or clinical interest events report~~ must be recorded in the electronic Case Report Form (eCRF) within 24 hours of ~~first knowledge~~**becoming aware** of the event. In case event requires immediate reporting but the EDC system (eCRF) is not functioning, the site should use the relevant paper forms and ~~fax~~ **email them to safety@urogen.com** ~~to the sponsor~~ within 24 hours of site being made aware of the serious adverse event. ~~Fax no. for events reporting: 00-972-77-4171410, Attn.: Dr. Michal Jeshurun, QPPV~~."

Section Updated	Protocol Version 5.0 Original Text	Protocol Version 6.0 Description of Change / New Text
	aware of the serious adverse event. *Fax no. for events reporting: 00-972-77-4171410, Attn.: Dr. Michal Jeshurun, QPPV.'*	
19.2.3. Special Reporting Situations	*" 19.2.3. Special Reporting Situations /Events of Clinical Interest"; " Safety events of interest on a sponsor medicinal product…"*	Updated: " 19.2.3. Special Reporting Situations ~~*/Events of Clinical Interest*~~ "; "~~Safety events of interest on~~Sponsor ~~a sponsor~~ medicinal product…"
19.2.4. Events of special interest	*" 19.2.4. In addition, the following adverse events are defined as "events of special interest":"*	Updated:" 19.2.4. ~~In addition, the following adverse events are defined as "e~~**E**vents of special interest~~":~~"; Added to bullet #8:"**Any of these Events of Special Interest that also meet criteria of Serious Adverse Event should be reported as such. These events will be evaluated and reviewed by the Sponsor pharmacovigilance team.**"
19.2.4 Events of special interest	*19.2.4 bullet 3* *"Symptoms suspicious of ureteral perforation/rupture – (prolonged localized abdominal or flank pain, abdominal tenderness/acute abdomen);"*	Revised 19.2.4 - bullet 3 Ureteral events, including stenosis, as well as symptoms suspicious of ureteral perforation/rupture – (prolonged localized abdominal or flank pain, abdominal tenderness/acute abdomen);
19.2.5- Management of Anomalies in Laboratory Parameters	*The investigator must review the patient's lab results and evaluate ~~the clinical meaning of~~ all anomalous laboratory ~~values based on the definition of standard values used by leading laboratories and CTCAE. Each~~ clinically significant ~~anomaly must be fully reported. "Clinically Significant" means any anomaly which, according to the investigator, represents a significant clinical problem, which requires medical attention or which otherwise falls under the definition of "Serious" adverse event. When clinically advised, additional tests or evaluations should be carried out to determine the significance or etiology of an anomalous result or to monitor the course of an adverse event. Any persistent anomalous value must be monitored at the investigator's discretion~~. Clinically significant ~~anomalous~~ results must be recorded in the relevant section of the eCRF.*	Revised: 'The investigator must review the patient's lab results and evaluate all anomalous laboratory values as clinically significant or not. Clinically significant results must be recorded as adverse events in the relevant section of the eCRF".
19.2.7. Concomitant Illnesses and Pre-existing Conditions		Added:"**Ongoing medical conditions and past cancer history other than urothelilal carcinoma, and significant medical history up to 5 years back from screening must be collected and recorded in the eCRF.**"
19.2.8. Adverse Events Reporting Period	*" The investigator is required to report all non-serious adverse events/ occurring starting with*	Re-edited and updated: " • The investigator is required to ~~report~~ **collect** ~~all non-serious adverse events/ occurring~~**AEs starting** beginning with informed consent

Section Updated	Protocol Version 5.0 Original Text	Protocol Version 6.0 Description of Change / New Text
	informed consent signing and up to 30 days post last instillation visit to the sponsor. This information is to be entered into the eCRF. • *In case of complete response patients continuing with maintenance treatments - Adverse events will be collected up to 30 days post last maintenance instillation and will be documented in the eCRF.* • *In case of non-complete response patients - All adverse events should be recorded up to the PDE Visit (5 weeks after the last instillation).* • *All serious adverse events, all AEs which are suspected to be related to the study treatment and/or procedures occurring during the trial period should be reported at all times."*	~~signing~~ **signature**. ~~and up to 30 days post last instillation visit to the sponsor.~~ This information is to be entered into the eCRF. • **All serious adverse events, aand All AEs which are suspected to be related to the study treatment and/or procedures occurring during the trial period should be reported at all times**. • ~~In case of complete response patients continuing with maintenance treatments -~~ Adverse events will be collected up to 30 days post last maintenance instillation or until resolution, and will be documented in the eCRF. • In case of non-complete response patients - All adverse events should be recorded up to the PDE Visit or until resolution (5 weeks after the last instillation). ~~All serious adverse events, all AEs which are suspected to be related to the study treatment and/or procedures occurring during the trial period should be reported at all times.~~ ~~• In case of complete response patients continuing with maintenance treatments - Adverse events will be collected up to 30 days post last maintenance instillation and will be documented in the eCRF.~~ ~~• In case of non-complete response patients - All adverse events should be recorded up to the PDE Visit (5 weeks after the last instillation).~~ ~~• All serious adverse events, all AEs which are suspected to be related to the study treatment and/or procedures occurring during the trial period should be reported at all times.~~"
20. Concomitant Medications		Added:" **Concomitant medications given to treat a reported adverse event must be recorded in the eCRF.**"
Appendix III: Required Lab Tests	*" Hematology Tests ** • *Complete blood count, including red blood cell indices and white blood cell differential* *Note: On visits where only CBC is required, it may be performed at the community but less recommendable.* • *Platelet count"*	Deleted:" " Hematology Tests * • Complete blood count, including red blood cell indices and white blood cell differential ~~Note: On visits where only CBC is required, it may be performed at the community but less recommendable.~~ • Platelet count""

Action Name	User Name	Title	Signature Date
Review	Ifat Klein	Director of Clinical Operations	29-May-2018 18:27 (GMT+2)
Review	Gilad Bernadsky	VP QA	29-May-2018 18:49 (GMT+2)
Send for Approval	Gilad Bernadsky	VP QA	29-May-2018 19:00 (GMT+2)
Send for Approval	Gilad Bernadsky	VP QA	14-Jun-2018 15:31 (GMT+2)
Send for Approval	Gilad Bernadsky	VP QA	14-Jun-2018 17:13 (GMT+2)
Send for Approval	Gilad Bernadsky	VP QA	18-Jun-2018 13:40 (GMT+2)
Approve	Jim Ottinger	VP Regulation	18-Jun-2018 14:52 (GMT+2)
Approve	Michal Jeshurun	Chief Scientific and Medical affairs	18-Jun-2018 15:23 (GMT+2)
Approve	Elyse Seltzer	SVP Clinical	18-Jun-2018 19:48 (GMT+2)
Approve	Gilad Bernadsky	VP QA	18-Jun-2018 20:43 (GMT+2)
QA Approve Without Training	Gilad Bernadsky	VP QA	18-Jun-2018 20:43 (GMT+2)