Statistical Analysis Plan

UroGen Pharma Ltd.

A Phase 3 Multicenter Study Evaluating the Efficacy and Safety of UGN-101 on Ablation of Upper Urinary Tract Urothelial Carcinoma

Final/Amendment 1

Final: 17 June 2019

Amendment 1: 27 April 2020

Signature Page

Written by:

Amendment 1 Version:	
Signature: _____ Date: _____ [redacted] Lead Biostatistician [redacted]	Signature: _____ Date: _____ [redacted] Senior Reviewer [redacted]

Sponsor Signature:

The undersigned hereby declare that they have examined the Statistical Analysis Plan document and agree to its form and content.

Represented by:

Signature: _____ Date: _____ [redacted] SVP Clinical Development UroGen Pharma Ltd.	Signature: _____ Date: _____ [redacted] Sr. Director, Biostatistics UroGen Pharma Ltd.

Version History

Version Number	Date	Revision
1.8	**27 April 2017**	**Final (Signed)**
2.0	**17 June 2019**	**Final**
2.1	**27 April 2020**	**Amendment 1**

Table of Contents

List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under Curve
CBC	Complete Blood Count
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Computed Tomography-Urography
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
FU	Follow-Up
HG	High Grade
HR	Heart Rate
ITT	Intent-to-Treat
LG	Low Grade
LOQ	Limit of Quantitation
mITT	Modified Intent-to-Treat
MMC	Mitomycin C
NIH	National Institutes of Health
PCS	Potentially Clinically Significant
PDE	Primary Disease Evaluation
PDECR	Complete Responder at the PDE visit
PG	Performance Goal
PK	Pharmacokinetic
PP	Per Protocol
RNU	Radical Nephro-Ureterectomy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOC	System Organ Class
TCC	Transitional Cell Carcinoma
UPJ	Uretero-Pelvic Junction
URS	Ureteroscopy
UTUC	Upper Tract Urothelial Carcinoma
UUT	Upper Urinary Tract
VAS	Visual Analog Scale

1 Introduction

1.1 General

Upper tract urothelial carcinomas (UTUCs) are malignant changes of the transitional urothelial cells lining of the upper urinary tract. The current gold standard of care for UTUCs patients with a normally functioning contra lateral kidney is radical nephro-ureterectomy (RNU) with excision of bladder cuff.

Urogen Pharma developed the investigational product for UTUCs patients that is presented in UGN-101 Kit comprising Mitomycin C (MMC) for injection drug product (the active component), and TC-3 Sterile Hydrogel. The proprietary gel (TC-3), allows for a sustained release of MMC at the target site of administration, resulting in prolonged exposure of the tumor cells to MMC, where it exerts the chemical ablative effect.

The main objective of this Phase III trial is to evaluate the efficacy and safety of UGN-101 on ablation of UTUC.

This document is based on the protocol version V6.0 (dated 18 June 2018) and contains updates from the previous statistical analysis plan (SAP) signed version (V1.8).

SAP Amendment is on the protocol version V6.0 (dated 18 June 2018) and includes revisions from the previous SAP signed version2.0 dated 17 June 2019. A summary of changes in SAP Amendment 1 is included in Section 15.

1.2 Study Design Configuration

This is a phase III, prospective, single-arm study designed to assess the efficacy, safety, and tolerability of treatment with UGN-101 instilled in the upper urinary system of patients with non-invasive low-grade, UTUC.

Upon signing of informed consent, the patients will undergo a screening visit for eligibility evaluation. Eligible patients will be treated with UGN-101 once weekly for a total of 6 times in a retrograde fashion. Patients who demonstrate complete response (CR) will be treated with UGN-101 once monthly as maintenance.

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).

2 Centers

This is a multicenter study, planning to include about 45-50 medical sites across the United States, Canada, and Israel.

3 Study Objectives

3.1 Safety Objective

Safety objectives include:

- Evaluation of safety and tolerability of the UGN-101 admixture in UTUC patients.
- Assessment of the pharmacokinetics profile of Mitomycin C (MMC) in plasma of a sub-group of patients treated with UGN-101 admixture.

3.2 Primary Efficacy Objective

The study's primary efficacy objective is to evaluate the tumor ablative effect of UGN-101 admixture in the upper urinary tract (UUT) of patients with UTUC at PDE visit.

3.3 Key Secondary Efficacy Objective

The study's key secondary efficacy objective is to evaluate response durability at 12-months follow-up for patients showing CR at PDE visit

3.4 Secondary Efficacy Objectives

The study's secondary efficacy objectives are

- To evaluate the durability of tumor ablative effect of UGN-101 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 UGN-101 admixture.

4 Treatment Groups

This is a single arm study where all eligible patients will be treated with investigational product - UGN-101.

5 Sample Size Rationale

Sample size determination was performed under the following assumptions:

- The primary efficacy endpoint of the study is the Complete Response rate at the PDE Visit;
- It is expected that the true CR rate following treatment with UGN-101 is 30% or more;
- The primary analysis of the primary endpoint will aim to rule out a threshold rate of 15% using a two-tailed 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 size 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 at least 83 patients will participate in this study.

6 Study Schedule

Table 1 Part I - All Patients - Up to PDE Visit

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**
Informed consent	X									
Demographics	X									
General and Urothelial Carcinoma Medical History, Smoking	X									
Concomitant Medications Review	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.

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**
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
CBC, liver and renal function, coagulation **	X	X♣	X♣	X♣	X♣	X♣	X♣	X♣ coags not required	X♣ coags not required	X
Urinalysis/dipstick	X	X	X	X	X	X	X			X

§ Investigator and sponsor confirmation of eligibility prior to instillation. Entry into the trial will be based on the local pathologist diagnosis.

Tx = Treatment; d = day; Wk/w = week

♠ Vital signs: Body temperature, blood pressure, heart rate, height and weight (screening)

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

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**
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

†† 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

Tx = Treatment; d = day; Wk/w = week; CBC = Complete Blood Count; CTU = Computerized Tomography (CT) Urogram; MRI = Magnetic Resonance Imaging

§§ 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**
Pregnancy urine test		X	X	X	X	X	X			X
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									

§§§ 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

Tx = Treatment; d = day; Wk/w = week

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**
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™ (UGN-101) Admixture administration		X	X	X	X	X	X			
VAS for pain evaluation		X	X	X	X	X	X			

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**
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			

**** In 6 treated patients

†††† Prior to instillation, 30min., 1, 2, 3, 4, 5, and 6 hours post instillation

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**
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 §§§§

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

Tx = Treatment; d = day; Wk/w = week

Table 2 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 Study 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

***** 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

Tx = Treatment; d = day; Wk/w = week; Maint = Maintenance; FU= Follow-up; CBC = Complete Blood Count

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 Study Completion**
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
Upper Urinary Tract Urine cytology-washing			X			X			X			X

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 Study Completion**
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	

†††††† 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 Study Completion**
Cystoscopy for catheterization	X	X	X	X	X	X	X	X	X	X	X	
MitoGel™ (UGN-101)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	

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 Study 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

***** Time windows for study visits V10, V12, V15, V18, V21 ±2 weeks.

7 Analysis Sets

7.1 Safety Analysis Set

The Safety analysis set will consist of all patients who enrolled in the study and received at least 1 instillation of UGN-101.
Specifically, this set will include all patients for whom the Case Report Form (CRF) item "Was the Instillation performed" is marked as "Yes" at least once.

7.2 Pharmacokinetic (PK) Set

The pharmacokinetic (PK) set will consist of all patients who signed the consent for PK and have sufficient data for the determination of PK parameters.
The PK data will be provided by the Sponsor as an external dataset.

7.3 Efficacy Analysis Sets

7.3.1 Main Efficacy Analysis Set

7.3.1.1 Intent-to-Treat (ITT) Analysis Set

The intent-to-treat (ITT) analysis set will consist of all patients enrolled in the study and have received at least one instillation of UGN-101.
Therefore, the ITT analysis set is identical to the Safety analysis set.

Treatment of Missing Values in ITT Analysis Set:

ITT patients with no observed value on primary efficacy will be imputed "Failure" for the primary efficacy endpoint. Note that this only affects patients who dropped out from the study before the PDE evaluation. In other words, patients with indeterminate results at the PDE visit but found to be CR at subsequent visits will be considered as CR at PDE also and will not be imputed as “Failure” for the primary efficacy analysis based on the ITT analysis set.
Note: Throughout this document, "indeterminate results" will refer to "undetermined" response recorded on the CRF or unavailable results.
Treatment of missing values for the key secondary endpoint is detailed in Section 8.4.

7.3.2 Additional Efficacy Analysis Sets Based on Local Lab Outcomes

7.3.2.1 Modified Intent-to-Treat (mITT) Analysis Set

The modified intent-to-treat (mITT) analysis set will be a subset of the ITT analysis set who have a valid response evaluation at PDE and / or re-evaluation visit (i.e. provide a clinical result and are not indeterminate). Patients with indeterminate results at PDE but found to be CR at subsequent visits will be considered as CR at PDE also and will be included in the mITT analysis set.

Treatment of Missing Values in mITT: Analysis Set:

By the analysis set definition, no missing primary outcomes are possible. Thus, only observed primary endpoint values will be used.

7.3.2.2 Per Protocol Analysis Set 1 (PP1)

The Per Protocol analysis set 1 (PP1) is a subset of the mITT analysis set and will consist of all enrolled patients who received ***at least four*** (4) UGN-101 instillations. Patients who are identified as high grade (HG) by local lab at the PDE visit will be excluded from the PP1 analysis set.

Treatment of Missing Values in PP1: Analysis Set:

Only observed values will be used in PP1 analysis set; i.e. missing data will not be imputed.

7.3.2.3 Per Protocol Analysis Set 2 (PP2)

The Per Protocol analysis set 2 (PP2) is a subset of the PP1 analysis set and will consist of all enrolled patients who received ***a total of six*** (6) UGN-101 instillations, who do not have major protocol deviations that could potentially affect the study efficacy outcomes. The listing of major protocol deviations will be provided by the Sponsor prior to the database lock.

Treatment of Missing Values in PP2 Analysis Set:

Only observed values will be used in PP2 analysis set; i.e. missing data will not be imputed.

7.3.2.4 Complete Responder at the PDE Visit (PDE_{CR}) Analysis Set

The complete responder at the PDE visit (PDECR) analysis set is a subset of the ITT analysis set that will include all patients who are CR at the PDE visit based on the local laboratory evaluations (see the definition of CR at PDE in Section 8.3).

Patients with UUT Cytology = 'Suspicious for High Grade Urothelial Carcinoma' at PDE visit from both local and central labs are excluded from PDE_{CR}. analysis set.

Treatment of Missing Values in PDE_{CR}: Analysis Set:

The PDE_{CR} analysis set is used to analyze the durability of CR summarized as time-to recurrence and as recurrence incidence.

Recurrence-free survival (or time to recurrence) at 12 month will be analyzed using Kaplan-Meier method. The censoring rule is provided in the following table:

	Status	Date of censor/event
Patients who discontinued prior to first follow-up visit after PDE evaluation	Censored	Date of PDE visit
Patients who died without disease recurrence after PDE visit	Censored	Date of death
Patients who had at least one follow-up visit and completed or discontinued without disease recurrence	Censored	Date of the last assessment
Patients who recurred	Event	Date of recurrence

Time to recurrence will be defined as date of censor or event – start study day for recurrence + 1.

The start study day for time-to-recurrence is the study day (date) when patients had an actual CR response, i.e., the study day of the repeated evaluation for the patients with indeterminate results at PDE but found to be CR at repeated evaluation visit.

Recurrence incidence, which serves as a supportive efficacy analysis, will not have missing data imputed; i.e. only observed data will be used. At the same time, patients with indeterminate results but found to be CR at subsequent visits will be considered as CR at the prior visits as well. It should be noted that such cases are not considered imputation of missing data, as clinically their status is known (retrospectively). Additionally, a tipping point sensitivity analysis may be performed for each time point separately if indicated by the data.

7.3.3 Additional Efficacy Analysis Sets Based on Central Lab Outcomes

7.3.3.1 Central Modified Intent-to-Treat (Central - mITT) Analysis Set

The central modified intent to treat (Central - mITT) analysis set is a subset of the ITT analysis set with confirmed LG UTUC at Screening by *central* lab and who have a PDE evaluation of response by the central lab.

Treatment of Missing Values in Central – mITT Analysis Set:

By the analysis set definition, no missing primary outcomes are possible. Thus, only observed values will be used.

8 Definition of Endpoints

8.1 Safety Endpoints

Safety endpoints will include:

- Treatment-emergent adverse events (AEs) and serious AEs (SAEs)
- AEs of special interest (AESIs) (see addendum of such AEs, prepared and appended prior to database lock)
- Laboratory test results
- Vital signs
- Full physical examination and urology-oriented examination
- Adverse events leading to discontinuation of study drug
- Pain during the instillation procedure assessed by Visual Analog Scale (VAS)
- Concomitant medications use

8.2 Pharmacokinetic (PK) Endpoints

The following PK parameters will be assessed:

- Cmax — maximum plasma concentration
- Tmax — time to maximum plasma concentration
- AUC(0-t) — area under the plasma concentration-time curve from 0 to final time with a concentration ≥ limit of quantitation (LOQ)

  Area under the curve to the final sample with a concentration ≥ LOQ will be calculated using the linear trapezoidal method

If data allows the following parameters will calculated as well:

- λz— elimination rate constant

  The elimination rate constant, λz, will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The slope will be determined from a plot of the natural log of the terminal plasma concentrations against time; at least 3 terminal plasma concentration time points, beginning with the final concentration ≥ LOQ and not including Cmax, will be selected for the determination of λz; the regression will have a coefficient of determination $R^2 \geq 0.9000$.
- Half-life (t½) — terminal half-life

$$t½ = 0.693 / \lambda z$$

- AUC(inf) — AUC extrapolated to infinity

$$AUC(inf) = AUC(0\text{-}t) + C(last) / \lambda z,$$

where C(last) is the final concentration ≥ LOQ.

8.3 Primary Efficacy Endpoint

The primary efficacy endpoint is CR defined for each patient dichotomously at PDE visit (CRF form "Evaluation of Response (Target Area Lesions) (PDE)".

The evaluation of response will be based on the *local* laboratory.
In more details:

- If "Evaluation of Response" at PDE visit is marked as "Complete Response" the CR is defined as 1 ("Success")
- If "Evaluation of Response" at PDE visit is marked as "Partial Response" or "No Response" the CR is defined as 0 ("Failure")
- If "Evaluation of Response" at PDE visit is marked as "HG Patient"
    - For ITT and mITT analysis sets, a patient is considered as non-CR ("Failure")
    - For the per-protocol analysis sets, the patient will be excluded from the analysis
- If "Evaluation of Response" at PDE visit is marked as "Undetermined" check the repeated evaluation (CRF form "Evaluation of Response (Target Area Lesions) (Repeated Evaluation)")
    - The repeated evaluation must be performed before the first maintenance treatment is done. If a patient was not re-evaluated before the first maintenance treatment or marked as “Undetermined”, the patient will be considered a failure (CR=0).
      Note: If re-evaluation and first maintenance are scheduled on the same date, the re-evaluation will always happen before the maintenance treatment.
    - If "Evaluation of Response" at re-evaluation visit is marked as "Complete Response" the CR is defined as 1 ("Success"),
    - If "Evaluation of Response" at re-evaluation visit is marked as "Partial Response" or "No Response" the CR is defined as 0 ("Failure")

- If "Evaluation of Response" at re-evaluation visit is marked as "HG Patient," the CR is defined dependent on the analysis set, as detailed above.
- If patient response is “Undetermined” or missing at PDE visit but the patient arrived to a later study follow-up visit (prior to receiving any maintenance treatments), the response determined at that follow-up visit will be imputed backward to the PDE visit.

For patients with UUT Cytology = 'Suspicious for High Grade Urothelial Carcinoma' from both local and central labs CR is defined as 0 ("Failure"). Primary endpoint will be considered missing only if a patient discontinues the study before achieving the PDE visit. Treatment of indeterminate results is addressed in Section 7.

8.4 Key Secondary Efficacy Endpoint

Long-term durability of CR is defined only for patients who achieved CR at PDE visit. Thus, long-term durability will be analyzed using PDE_{CR} analysis set. Long-term durability of CR will be defined in two ways:

1. Continuously: Duration of CR or time-to recurrence since the PDE visit (i.e. time in days from the visit at which CR was determined until recurrence or censoring). The analysis for this endpoint will serve as the primary analysis to assess and describe the long-term durability endpoint.
2. Dichotomously: "Success" if CR was still present at 12 months post PDE visit (at follow-up visit 4), and "Failure" otherwise. The analysis for this endpoint will serve as a supportive approach to describe the long-term durability endpoint, but will be the endpoint considered for the hypothesis testing for the key secondary endpoint as defined in the protocol.

The dichotomous endpoint is defined based on the CRF form "Complete Response Durability Assessment".

The evaluation of the patient for CR durability will be based on local laboratory results.

Although the key secondary endpoint for recurrence incidence is defined for the 12-month visit, the following definition for the recurrence incidence will be applied to all time points separately (3, 6, 9, 12 months follow-up, and all unscheduled visits).

- If "Complete Response Durability Assessment" at any follow-up visit is marked as "Urothelial carcinoma recurrence at the target area" or "Urothelial carcinoma progression at the target area" (at least once), all subsequent follow-up visits are defined as 0 ("Failure"/recurrence event).
- If "Complete Response Durability Assessment" at any follow-up visit is marked as "Durable complete response at target area," all previous follow-up visits with missing assessment of durability of CR or indeterminate response are defined as CR (“Success”/no recurrence).
- If "Complete Response Durability Assessment" at follow-up visit 4 is indeterminate (i.e. marked as "Undetermined" on CRF or not evaluated) check the repeated evaluation (unscheduled visit)
    - If "Complete Response Durability Assessment" at re-evaluation visit is marked as "Complete Response" (i.e. at the target area) the long-term durability of CR is defined as 1 ("Success"/no recurrence).
    - Otherwise, the measure is not valid; i.e. is considered missing for analysis.

8.5 Secondary Efficacy Endpoint

Durability of CR for each follow-up time point separately is defined in the preceding section.

Clinical Benefit for Patients with Partial Response at PDE Visit

Clinical benefit endpoint will be analyzed using the ITT analysis set including patients who achieved partial response at PDE visit.
The clinical benefit endpoint is evaluated by the following:

- Originally planned treatment (CRF form "Planned UTUC Treatment prior to Study (Screening)")
- Whether the planned treatment changed (the CRF item "Has the UTUC treatment plan for the target lesions, above the uretero-pelvic junction (UPJ), changed compared to planed treatment prior to study?"
- Actual treatment (the CRF item "If ‘Yes’, please specify current treatment plan").

9 Data Derivation and Transformation

Data not originally part of the CRF will be derived as follows:

- Age (years) = [Date of Informed Consent – Date of Birth] / 365.25
- BMI = Weight (kg) / Height $(m)^2$
- Temperature [F°] = (9/5) × Temperature [C°] + 32
- Coding of Adverse Events will be done using MedDRA version 19.1.
- Coding of Concomitant Medication will be done using the WHODrug Dictionary (version September 2016).
- Baseline refers to the last available observation prior to initiation of treatment (including at the treatment 1 visit but prior to treatment) unless noted otherwise.
- Severity of adverse events was coded by sites using NIH CTCAE version 4.03.
- Abnormal laboratory results will be coded using NIH CTCAE version 5.0.

10 Interim Analysis

An independent Data Monitoring Committee (DMC) is assigned for this study. 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 **futility** analysis will be conducted after N = 20 evaluable patients 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 who will than make the final determination on study continuation.

An interim clinical study report including efficacy and safety analysis results will be prepared using an early data cut-off. At the time of this early data cut-off, all patients would have completed the treatment period and most would have completed the maintenance phase.

11 Statistical Analysis

All descriptive statistics will be provided by visit (if relevant) and overall. Numerical variables will be tabulated using mean, standard deviation, minimum, median, maximum and number of observations. Categorical variables will be tabulated using number of observations and percentages. Time-to variables will be analyzed using Kaplan-Meier method and descriptive statistics as appropriate.

11.1 Patient Disposition

The following will be provided:

- Number and percentage of patients in each of the analysis sets by site and overall. Only sites with patients which received treatment will be included in this summary. That is, the table will be based on the Safety analysis set. Percentages will be calculated out of number of patients in Safety analysis set for each site.
- Listing of enrolled patients excluded from each analysis set along with reason for exclusion.
- Frequency distribution of enrolled patients excluded from each analysis set by reason for exclusion.
- Frequency distribution of reason for screen failure (based on patient eligibility by site investigator, or on patient eligibility by the sponsor, in case that that patient was eligible by the investigator).
- Summary of patient disposition table, including frequency distribution of screened, enrolled, treated and not treated, per-protocol study completion (based on study termination CRF form), ongoing within the study (i.e. all patients who have not completed the study termination CRF form), study early termination (i.e. patients who did not complete study per-protocol according to the study termination CRF form), treatment early termination (based on treatment early termination CRF form) and patients with partial maintenance treatment (i.e. began but not completed maintenance period; PDE_{CR} analysis set).
- By-patient listing of early treatment termination, including the screening number, number of instillations received, time since enrollment (days) and reason for termination (Safety analysis set).

- By-patient listing of maintenance early treatment termination, including the screening number, number of maintenance instillations received, time since PDE visit (days) and reason for termination (PDE_{CR} analysis set).
- By-patient listing of early study termination, including the screening number, time since enrollment (days) and reason for study termination (Safety analysis set).
- By-patient listing of all protocol deviations (Safety analysis set)
- Frequency distribution of protocol deviations by the following types: study eligibility, study conduct and patient management, and severity (major / minor).
- By-patient listing of screen failures including reason for screen failure.

11.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized using the ITT analysis set.

Descriptive statistics will be provided for the following:

Demographic characteristics

- Summary of baseline characteristics including, Age and Age groups (<65, 65-74 and ≥75 years), Sex, Race, Height, Weight, BMI and BMI groups (≤30 and >30 kg/m^2).
- Number and percent of patients who are never, current or past smokers.

General Medical History, Prior (Past) and Concomitant Medications

- Number and percent of patients who have any known medical conditions, by MedDRA V19.1 System Organ Class (SOC) and by preferred term (PT) in descending frequency order within each SOC.
  A patient with multiple conditions will be counted once per SOC/PT combination.
- Frequency distribution of patient's number of kidneys.
- By-patient listing of patient's number of kidneys.
- By-patient listing of general medical history including patient screening number, reported term for the medical history, MedDRA term, SOC, Start Date, End Date or whether ongoing, and whether the patient received therapy for this medical condition.
- Frequency distribution of concomitant medications not related to urothelial carcinoma (i.e. not marked as "past and concurrent urothelial carcinoma medical history" on the "Past and Concomitant Therapies" CRF form and with end date after start of treatment), by WHODrug dictionary (version September 2016) ATC class and medication name. Summary results will be presented in descending order of frequency.
- Frequency distribution of any prior or concomitant medications related to urothelial carcinoma medical history (irrespective of dates of start or end).
- Frequency distribution of prior procedures and surgeries according to the same classifications as the previous two bullets regarding medications.

Prior (past) and concomitant medications (as collected on the Past and Concomitant Therapies CRF form) will be presented in two by-patient listings:

(1) By-patient listing of all medications where the CRF item "indication related to" is ***not*** answered by "Past and Concurrent Urothelial Carcinoma medical history, record number".
  This listing will include: Screening number, medication generic name or therapy, dose, start date, end date, whether ongoing, indication, and "indication related to".

(2) By-patient listing of all medications where the CRF item "indication related to" ***is*** answered by "Past and Concurrent Urothelial Carcinoma medical history, record number".

This listing will include: Screening number, medication generic name or therapy, frequency, start date, end date, whether ongoing, indication, and urothelial carcinoma treatment.

By-patient listing of all prior and concomitant procedures and surgeries (i.e. all non-medication therapies collected on the Past and Concomitant Therapies CRF form).

Past and Concurrent Urothelial Carcinoma Medical History (Screening, pre-debulking)

Number of Past Episodes Definition:
If a patient has several records with the **same start date** (for example, one record in upper tract and another record in bladder), these records will be counted as a **single** episode. If there are both current and past episodes with the same start date, the episodes are considered as a current episode and will not be counted as a past episode. An episode is considered as an "Upper Urinary Tract Episode" if it has at least one record in the UUT.

- Summary of past urothelial carcinoma, including frequency distribution for the number of any past episodes and UUT past episodes obtained per patient (not including the current episode).

Number of Papillary Lesions

- Summary of Papillary Lesions for the current upper urinary tract episode with at least one lesion located above UPJ, including descriptive statistics for:
    - Number of papillary lesions
      If more than 1 episode in the same location (above the UPJ or below the UPJ) was marked as current episode, the number of lesions, diameter of largest tumor and the tumor burden within the location will be calculated according to the largest record available for each of these parameters.
    - Diameter of the largest papillary tumor for the current UUT episode (mm)
      If more than one UUT record within the current episode exists, the Largest Papillary Tumor Largest Diameter is defined as the maximum over all reported largest diameter (located either above or below UPJ).
    - Total tumor burden of the current UUT episode (mm)

- For each patient, if more than one UUT record within the current episode exists, the tumor burden is defined as the sum of all tumor burdens reported in the upper urinary tract (above UPJ or below UPJ).
- If at least one tumor burden in the UUT current episode (above UPJ or below UPJ) is missing, the total tumor burden of this episode will be considered missing.

o Whether tumor is unreachable by laser

Notes:

(1) The total N in this table counts the number of current UUT episodes with at least one lesion above the UPJ.

(2) For each patient, the number of lesions is defined as the sum of papillary lesions (in the current UUT episode) found above the UPJ and below the UPJ. Only the treated side (either left or right) will be considered in this analysis. The information about the treated side appears in the CRF form "Target Treatment Area Lesion Mapping – Information."

(3) Bladder lesions (if any exist) will be ignored in this analysis.

Target Treatment Area Lesion Mapping - Information

Number of papillary lesions, Largest diameter and Tumor Burden post debulking procedure will also be summarized.

ECOG & Karnofsky Scores at Screening

- Frequency distribution of ECOG performance status.
- Frequency distribution of Karnofsky performance status.

11.3 Pre-Treatment Medications

This analysis will be done using ITT and PDE$_{CR}$ analysis sets.

This analysis will be done separately for

a) Main treatment period of 6 instillations

b) Maintenance period of additional 11 instillations

- Frequency distribution of patients who consume 1.3 gr bicarbonate, by treatment visit and time point (the compliant answer is "Yes").

The table will also present the rate of patients who are 100% and at least 80% compliant with the pre-treatment requirement (where compliance is defined as taking all 3 pre-treatment doses for a given treatment).

- Frequency distribution of patients who receive a prophylactic antibiotic (the compliant answer is "Yes").
- The table will also present the rate of patients who are 100% and at least 80% compliant with the pre-treatment requirement (where compliance is defined as taking all 3 pre-treatment doses for a given treatment).

In addition, for the main treatment period by-item compliance will be defined as follows:

By-item compliance:

For each of the above items and for each patient, compliance percentage will be calculated as the number of doses of bicarbonate or antibiotic taken out of the total number of doses expected for each patient based on the number of treatments the patient received (i.e. out of the number of treatments among patients in the analysis set).

Descriptive statistics of the compliance percentage will be presented.

11.4 Treatment Procedure

This analysis will be done using ITT and PDE_{CR} analysis sets.

This analysis will be done separately for

a) Main treatment period of 6 instillations using ITT analysis set
b) Maintenance period of additional 11 instillations using PDE_{CR} analysis set

The following will be presented:

- Frequency distribution of mode of planned Instillation administration (identified based on CRF form "Pyelography and Planned Mode of Installation") (only for ITT analysis set)
- Descriptive statistics of the number of instillations performed per patient (derived based on CRF item "Was the instillation performed" is marked as "Yes").

Note: Information from unscheduled visits will be included. If treatment was done before the date of PDE, the unscheduled visit with a visit date prior to PDE visit will be counted as part of the main treatment period; otherwise, it will be counted as part of the maintenance period.

- Frequency distribution of the number of patients with actual volume different than planned.

  Note: Volume actually instilled is considered to be different if at least one reason for actual volume being different from the planned volume was fulfilled on the CRF.

- By-patient listing of all instillations where there is a difference between the planned and the actual volume instilled (including number of days since first treatment).
- By-patient listing of all instillations where ureteral catheter was **not** inserted, including the reason (A single J in-dwelling ureteral catheter is already inserted / Nephrostomy tube / Other).
- Frequency distribution of ureteral catheter diameter used (7 Fr / 5 Fr / Other). Exploratory analysis evaluating the effect of catheter size and diameter may be performed specifically for AESIs in the renal urinary SOC (see addendum to SAP with list of these AEs).
- Number and percentage of patients for whom general anesthesia was given, out of patients receiving treatment anytime and by visit during treatment and maintenance periods (separately).

11.5 Efficacy

11.5.1 PDE Response Evaluation

Frequency distribution of patient response at PDE (or repeated evaluation) will be presented based on **local** and **central** laboratory results. Local laboratory results will be presented based on the ITT analysis set and central laboratory results will be presented based on the Central – mITT analysis set.

11.5.2 Primary Efficacy Analysis

Primary efficacy analysis will be done using the ITT analysis set.

The primary efficacy analysis will test the following hypotheses:

H_0: CR rate at PDE ≤ 15%

H_1: CR rate at PDE > 15%.

Testing will be done by using an exact binomial *two-sided* hypothesis testing, with two-sided α= 0.05. (Note that this is identical to the one-sided test with α=0.025).

Assuming the sample includes 74 evaluable patients (the sample size planned in the protocol) the decision rule is: Reject the null hypothesis above if the number of CRs in the sample is at least 18.

If the number of evaluable patients will not be 74, the rejection area will be updated accordingly, using the same statistical methodology.

The following will be presented as a part of Primary efficacy analysis:

Number and percent of patients who are complete responders at PDE, along with 95% exact confidence interval, and exact binomial hypothesis testing p-value.

A sensitivity analysis will be performed to evaluate the robustness of the primary efficacy results using different assumptions for handling missing values and repeating the primary analysis on different analysis sets. Sensitivity analysis is detailed in Section 11.5.7.1.

11.5.3 Key Secondary Efficacy Analysis

The key secondary endpoint, durability of CR at 12 month, will be analyzed based on the PDE_{CR} analysis set.

The key secondary efficacy analysis for the dichotomous endpoint will test the following hypotheses using exact binomial test and PDE_{CR} analysis set:

H_0: Durable CR at 12-months ≤ 40%

H_1: Durable CR at 12-months > 40%.

where durable CR at 12-months is defined as percentage of patients in PDE_{CR} analysis set who are CR at 12 months. Success for this endpoint will be declared if the lower bound of the exact binomial 95% confidence interval for recurrence-free rate at 12 months is above 40%.

Recurrence-free survival rate at 12 month (continuous key secondary endpoint) defined as the probability of maintaining CR (i.e. remaining recurrence free) at 12 month. This will be estimated using Kaplan-Meier method. The standard error and 95% confidence interval of the estimate will be calculated using Greenwood's method.

In addition, the following will be presented:

- Summary of events and censoring
- Quartiles and median recurrence-free survival with the corresponding 95% confidence interval.
- Kaplan-Meier survival plot
- Life table from the Kaplan-Meier analysis, including monthly time point (0-12), number of patients at risk, number recurred and censored patients, estimated survival probability along with 95% confidence intervals.
- Descriptive statistics (mean, standard deviation, median, 1st and 3rd quartile, minimum, and maximum) for time (months) to recurrence computed as [Recurrence date – CR response date + 1]/30.4375

Additional summary results:

- Descriptive statistics (mean, standard deviation, median, 1st and 3rd quartile, minimum, and maximum) for duration of follow-up post PDE visit computed as [End of study date – CR response date + 1]/30.4375. This analysis will be based on PDE_{CR} analysis set.
- Descriptive statistics (mean, standard deviation, median, 1st and 3rd quartile, minimum, and maximum) for duration of study follow-up computed as [End of study date – first dose date + 1]/30.4375. This analysis will be based on ITT analysis set.

The analysis using dichotomous durability of CR will include:

- Frequency distribution of dichotomous observed long-term durability of CR, along with a two-sided 95% exact binomial confidence interval.

A sensitivity tipping point analysis may be performed to evaluate the robustness of the dichotomous key secondary efficacy results if indicated by the data, as detailed in Section 11.5.7.3.

11.5.4 Secondary Efficacy Analysis

The first secondary endpoint—durability of CR at target area — will be analyzed using the PDE_{CR} analysis set.

Durability of CR

The following will be presented:

- Frequency distribution of patient response evaluation at follow-up visits based on observed local and central laboratory results. If there is more than 1 response by central laboratory within an analysis visit, the results from the same visit as the local laboratory analysis will be used. In other words, the selection of the analysis visits for the central laboratory results is based on the local laboratory results.
- Frequency distribution of dichotomous durability of CR at 3, 6 and 9 months post PDE (FU visits 1, 2 and 3), along with 95% exact confidence interval.
- Sensitivity tipping point analysis may be performed for dichotomous durability of CR for each time point separately, if indicated by the data.

Clinical Benefit for Patients with Partial Response at PDE Visit

The second secondary endpoint—Clinical Benefit—will be presented using ITT analysis set.

- By-patient listing of all patients who are partial response at PDE visit including patient ID, site, number of instillations received within the treatment period, planned UTUC treatment at screening, whether this treatment was changed, current treatment plan (if was changed).
- By-patient listing of the reason patients who were considered ineligible for endoscopic resection, included within the listing of Upper Tract Urothelial Carcinoma Treatments. These cases will be recorded in the Comments CRF form and will be filtered by the Sponsor based on investigators reports and/or via review of the patients' medical records.

11.5.5 Target Treatment Area Lesion Mapping

Target treatment area location mapping analysis will be done using ITT analysis set.

Target Treatment Area Lesion Mapping - Information

Summary of papillary lesions information, presented by visit and including the following (on a patient level): total number of papillary lesions, largest lesion diameter (mm), total tumor burden (as defined in Section 11.2).

11.5.6 Covariate (Subgroup) Analyses

These analyses will be performed to examine the effect of the following covariates on the primary and key secondary (continuous) endpoints. No p-values will be reported.

i. For the primary endpoint the covariate analysis will be done using ITT analysis set.
ii. For the key secondary endpoint (dichotomous and continuous) the covariate analysis will be performed using PDE_{CR} analysis set.

The following covariates (subgroups) will be examined.

- Age (years): <65, 65-74 and ≥75.
- Gender
- BMI (≤30 kg/m^2 and >30 kg/m^2)
- Country (US/Israel)
- Site - If many sites will include a small number of patients, the analysis will be done descriptively
- Largest Diameter (pre- and post-debulking) at Screening
  Largest diameter is defined as the maximum within a patient over all diameters of papillary lesions reported in the CRF Urothelial Carcinoma Medical History CRF form (for pre-debulking) and in "Target Treatment Area Lesion Mapping – Information (Screening)" CRF for post-debulking. The largest diameter will be divided into 2 categories: ≤ 1cm and > 1 cm.
- Number of papillary lesions (pre- and post-debulking) at Screening
  Number of papillary lesions is defined as the total number of lesions reported per patient in the CRF "Target Urothelial Carcinoma Medical History CRF form (for pre-debulking) and for post-debulking in CRF "Target Treatment Area Lesion Mapping – Information (Screening)". The number of papillary

lesions will be divided into 2 categories: a single lesion and more than 1 lesion.

- Number of previous upper urinary tract (UUT) episodes (zero versus at least one) based on Urothelial Carcinoma Medical History form.
- Tumor Burden (pre- and post-debulking) at Screening
  Tumor burden is calculated per patient as the sum over all lesions largest diameters of papillary lesions in the CRF "Target Urothelial Carcinoma Medical History CRF form (for pre-debulking) and in CRF "Target Treatment Area Lesion Mapping – Information (Screening)" for post-debulking. If at least one of lesion largest diameters within a patient is missing (was not measurable or unknown) the tumor burden of the patient will be considered missing.
  Tumor burden will be divided into two levels based on sample median value.
- Number of treatment/maintenance instillations received.
  - Number of treatments will also be divided into two categories: 6 treatments (full per-protocol course) and less than 6 treatments (partial course).
- Whether tumor is unreachable by laser (Yes / No)

Pre-debulking observations are based on Urothelial Carcinoma Medical History CRF form and post-debulking observations are based on Target Treatment Area Lesion Mapping CRF form.

Frequency and percentage of CR (primary endpoint) along with the exact 95% confidence interval will be presented for each of the above covariates (subgroups) using the ITT analysis set. The summary will also be displayed by a forest plot.

Frequency and percentage of durable CR (dichotomous key secondary endpoint) will be presented at 12 month time point, and separately at 3, 6, and 9–month time points along with the exact binomial 95% confidence interval for each of the above covariates (subgroups) using the PDE_{CR} analysis set. The summary for 12-month time point will also be displayed by a forest plot.

11.5.7 Sensitivity Analysis

Sensitivity analysis will be performed for the primary and the key secondary endpoints.

11.5.7.1 Primary Related Analysis

The primary analysis will be repeated using different analysis sets — mITT, PP1, PP2 and Central-mITT. No p values will be generated. The results will also be displayed by a forest plot.

11.5.7.2 Primary Endpoint Missing Values Sensitivity Analysis

For the primary analysis, patients who do not have a PDE visit (early study termination) for any reason, will be 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 may be applied if indicated by the data.

This analysis will start by imputing all missing patients (early terminations) as "Success" (or Complete Responders). Then, at each step, the number of imputed "Successes" will be reduced by one and the number of imputed "Failures" will be increased by 1, until the case where all missing values are imputed as "Failure" (which is equivalent to the primary analysis). For each imputation scenario, exact binomial hypothesis testing p-value and 95% confidence interval will be reported. The summary presentation of tipping point analysis will include the best case scenario, worst case scenario and the tipping point from statistically significant to statistically non-significant results.

It should be noted that multiple imputation will not be performed as in the case of a binary endpoint tipping point analysis addresses all possible scenarios.

11.5.7.3 Dichotomous Key Secondary Endpoint Missing Values Sensitivity Analysis

For the dichotomous key secondary analysis, patients who did not complete the last FU visit and have no prior recurrence are not imputed. A sensitivity analysis will be done to examine the robustness of results if alternative imputation scenarios are used. Specifically, the tipping point imputation may be applied if indicated by the data.

This analysis will start by imputing all missing patients (early terminations) as "Success" (or CR). Then, at each step, the number of imputed "Success" will be reduced by one and the number of imputed "Failure" will be increased by 1, until the case where all missing values are imputed as "Failure" (which is equivalent to the primary analysis). For each imputation scenario, exact binomial hypothesis testing p-value and 95% confidence interval will be reported.
The summary presentation of tipping point analysis will include the best case scenario, worst case scenario and the tipping point from statistically significant to statistically non-significant results.

11.5.8 Long-Term Extended Follow-Up

Following the FDA request, patients with CR at PDE will be followed-up beyond the initial 12 months planned in the protocol for data of bladder urothelial carcinoma occurrence/recurrence and upper tract urothelial carcinoma recurrence, progression, and occurrence of invasive disease and radical nephroureterectomy. These data will be presented and summarized descriptively.

11.6 Cytology and Histopathology Results

11.6.1 Cytology Results

CRF form "UUT Cytology- **Local** Lab Results (Screening / PDE / FU / unscheduled)"

- Frequency distribution of the classification tool used in local laboratory, by visit. (Paris Classification (New), Bethesda Classification (Older), Other)
- Frequency distribution of diagnosis, by visit

Note that the two tools will be combined into a single output. The combination is done based on the following:

Table 3 Cytology Paris and Bethesda Classifications Combined Results

Combined cytology results	According to on Paris Classification	According to Bethesda Classification
Non-diagnostic/Unsatisfactory	Non-diagnostic/Unsatisfactory	
Negative for High Grade Urothelial Carcinoma (NHGUC) or Epithelial cell abnormality	Negative for High Grade Urothelial Carcinoma (NHGUC)	Negative for epithelial cell abnormality
Atypical Urothelial Cells	Atypical Urothelial Cells (AUC)	Atypical urothelial cells
Suspicious for High Grade Urothelial Carcinoma (SHGUC)	Suspicious for High Grade Urothelial Carcinoma (SHGUC)	
High Grade Urothelial Carcinoma (HGUC)	High Grade Urothelial Carcinoma (HGUC)	High-grade urothelial carcinoma
Low Grade Urothelial Neoplasm (LGUN)	Low Grade Urothelial Neoplasm (LGUN)	Low-grade urothelial carcinoma
Other/ Adenocarcinoma	Other: Primary and secondary malignancies and Miscellaneous lesions	1) Other, Any molecular Findings + 2) Adenocarcinoma

CRF form "UUT Cytology- **Central** Lab Results (Screening / PDE / FU)"

- Frequency distribution of test results, by visit

Local versus Central Diagnosis

- By-patient listing of discrepancies between local and central diagnosis results and patient response based on local and central laboratory (ITT analysis set)

11.6.2 Biopsy for Histopathology Results

Biopsy for Histopathology- **Local** laboratory results (Screening / PDE / FU)

- Frequency distribution of Histology Results, by visit

  If more than one option is chosen it will be defined as a separate category.

Biopsy for Histopathology- **Central** laboratory results (Screening / PDE / FU)

- Frequency distribution of Histology Results, by visit

  If more than one option is chosen it will be defined as a separate category

Local versus Central Diagnosis

- By-patient listing of discrepancies between local and central diagnosis results and patient response based on local and central laboratory (ITT analysis set)

11.7 Safety

All safety analyses will be performed on the safety analysis set.
The following will be provided:

11.7.1 Exposure

- Descriptive statistics of the volume (mL) of UGN-101 and Mitomycin to be instilled (auto-calculated in the CRF at Screening) (CRF form "Pyelography and Planned Mode of Installation"), or actually calculated and instilled at other visits. The table will also include the total UGN-101 volume instilled (per patient) over the course of participation (treatment and maintenance), to address the drug exposure.
- Frequency distribution for the number of treatment and maintenance instillations performed.
- Descriptive statistics for the length of exposure to study treatment (days) from the first instillation received.

11.7.2 Displays of Adverse Events

Summary of Adverse Events (AEs), including the incidence of all AEs, treatment emergent AEs, serious AEs (SAEs), serious adverse reactions (SAR; i.e. SAEs that are possibly, probably or definitely related to study drug), suspected unexpected serious adverse reaction (SUSAR) as determined based on Sponsor SAE reporting where event was both related and unexpected (expected AEs are listed in the Investigator's Brochure), AEs leading to treatment discontinuation, study drug or procedure related AEs leading to treatment discontinuation, AEs leading to death, drug related AEs, procedure related AEs, procedure related SAEs, drug or procedure related AEs, drug or procedure related SAEs.

AEs leading to treatment discontinuation are considered as such when the action taken is marked as 'drug permanently discontinued' or was marked as terminated from treatment due to this AE. An AE is considered related to study drug or study procedure when indicated in CRF to be possibly, probably or definitely related. Treatment emergent AEs are those occurring on or after the first day of study treatment. AEs with missing start date (both month and year) will be considered treatment emergent, unless the non-missing year indicates prior year before the

first dose date. Partial AE start dates (i.e., missing day) will be imputed as the 1st of the month. Partial AE end dates (i.e., missing day) will be imputed as the end of the month.

All Adverse Events

Tables specified below will be presented by:

(1) MedDRA V19.1 System Organ Class (SOC) and preferred term (PT)

(2) MedDRA V19.1 PT

- Incidence of patients with treatment emergent adverse events by maximal severity. The table will be presented in the descending frequency order.
- Incidence of patients with treatment emergent adverse events by maximal relationship to study *drug or procedure*. The table will be presented in the descending frequency order.
- Incidence of patients with treatment emergent adverse events by maximal relationship to study *drug*. The table will be presented in the descending frequency order.
- Incidence of patients with treatment emergent adverse events by maximal relationship to study *procedure*. The table will be presented in the descending frequency order.
- Incidence of patients with all grade and grade 3 or 4 adverse events.
- Summary of adverse events reported in >=10% (any grade) or >=5% (grade 3/4) of patients.
- Descriptive statistics of time to first AE leading to treatment interruption (temporary discontinuation) or treatment discontinuation (permanent discontinuation), as well as time to any treatment interruption and days from last treatment prior to the onset of the treatment discontinuation or any dose interruption (per event).
- Incidence of patients with treatment emergent adverse events leading to treatment discontinuation. The table will be presented in the descending frequency order.
- Incidence of patients with treatment emergent adverse events leading to death. The table will be presented in the descending frequency order.
- Number and percentage of patients with at least one AE by the following subgroups: Age group, sex, BMI group, renal function (baseline eGFR, <35,

35-45, 45-60, ≥60), center, number of kidneys, success on primary endpoint (CR at PDE), tumor debulking at baseline (at least one upper urinary tract episode was treated and marked as current based on Past and Concurrent Urothelial Carcinoma Medical History CRF form) and catheter size (categorized by percentage of treatments with 7 Fr used: 0%, 0%-50%, 50%-100%, 100%).

Serious Adverse Events

Tables specified below will be presented by
(1) MedDRA V19.1 SOC and PT
(2) MedDRA V19.1 PT

- Incidence of patients with treatment emergent *serious* adverse events maximal severity. The table will be presented in the descending frequency order.
- Incidence of patients with treatment emergent adverse events by maximal relationship to study *drug or procedure*. The table will be presented in the descending frequency order.
- Incidence of patients with treatment emergent *serious* adverse events by maximal relationship to study *drug*. The table will be presented in the descending frequency order.
- Incidence of patients with treatment emergent *serious* adverse events by maximal relationship to study *procedure*. The table will be presented in the descending frequency order.
- Descriptive statistics of time to first SAE leading to treatment interruption (temporary discontinuation) or treatment discontinuation (permanent discontinuation), as well as time to any treatment interruption and days from last treatment prior to the onset of the treatment discontinuation or any dose interruption (per event).
- Number and percentage of patients with at least one SAE by the following subgroups: Age group, sex, BMI group, renal function (baseline eGFR, <35, 35-45, 45-60, ≥60), center, number of kidneys, success on primary endpoint (CR at PDE), tumor debulking at baseline (at least one upper urinary tract episode was treated and marked as current) and catheter size (categorized by percentage of treatments with 7 Fr used: 0%, 0%-50%, 50%-100%, 100%).

Adverse Events of Special Interest (AESI)

A list of AESIs to be included in the tables described below will be provided by the Sponsor as an addendum to the SAP following their review and comparison to the criteria of such events as outlined in the study protocol.

- Summary table of all AESIs, presented in same way as the overall AE summary table.

The tables specified below will be presented by MedDRA V19.1 SOC and PT:

- Incidence of patients with all treatment emergent AESIs by maximal severity. The table will be presented in the descending frequency.
- Incidence of patients with treatment emergent AESIs by relationship to study drug. The table will be presented in the descending frequency.
- Summary of duration of stent for patients with adverse events of Urinary Tract Obstruction
- Incidence of patients with treatment emergent *serious* AESIs. The table will be presented in the descending frequency.
- Descriptive statistics for the onset of all treatment emergent and time to onset of first occurrence of treatment emergent AESIs in the Renal Urinary SOC by Preferred Term, including time from first instillation to start of AE , time from last treatment prior to the onset of the AE and number of instillations prior to AE.
- Number and percentage of patients with at least one AESI in the Renal Urinary SOC by the following subgroups: Age group, sex, BMI group, renal function (baseline eGFR, <35, 35-45, 45-60, ≥60), center, number of kidneys, success on primary endpoint (CR at PDE), tumor debulking at baseline (at least one upper urinary tract episode was treated and marked as current) and catheter size (categorized by percentage of treatments with 7 Fr used: 0%, 0%-50%, 50%-100%, 100%).
- Incidence of patients with treatment emergent AESIs in the Renal Urinary SOC by whether resolved, resolved with sequalae or ongoing.
- Number of instillations prior to onset of urinary obstruction adverse events with no documented resolution or resolved with sequelae.
- Incidence of patients with treatment emergent *serious* AESIs in the Renal Urinary SOC. The table will be presented in the descending frequency.

- Descriptive statistics for the onset of serious treatment emergent AESIs in the Renal Urinary SOC by Preferred Term, including time from first instillation to start of AE, time from last treatment prior to the onset of the AE and number of instillations prior to AE.
- Number and percentage of patients with at least one serious AESIs in the Renal Urinary SOC by the following subgroups: Age group, sex, BMI group, renal function (baseline eGFR, <35, 35-45, 45-60, ≥60), center, number of kidneys, success on primary endpoint (CR at PDE), tumor debulking at baseline (at least one upper urinary tract episode was treated and marked as current) and catheter size (categorized by percentage of treatments with 7 Fr used: 0%, 0%-50%, 50%-100%, 100%).
- Summary table of urinary tract narrowing events, including frequencies of narrowing events, patients experiencing pain, hydronephrosis identified, urine flow compromised, interventions performed as well as frequency of each of the interventions.

Treatment-Emergent Adverse Events Listings

- Listing of all AEs including Screening Number, AE description, mandatory treatment discontinuation, start date, stop date, frequency, severity grade, action taken, whether serious or not, whether SUSAR or not, action taken with study treatment, other actions taken to treat the event, relationship to study drug, relationship to the study procedure, specify related procedure, outcome, was patient terminated from Treatment due to this AE?
- Listing of all Serious Adverse Events as described in the previous bullet.
- Listing of all AEs leading to dose reduction, temporary or permanent discontinuation of study treatment or maintenance treatment. AE leading to permanent discontinuation is defined as AEs with "Action Taken with Study Treatment" marked as "permanently discontinued" AND AEs with "was patient terminated from Treatment due to this AE?" marked as "yes". This listing will include the information specified above as well as the number of treatment instillations received, the number of maintenance instillations received and the time to event (in days).
- Listing of AESIs including SOC, PT, severity, relationship and if it led to discontinuation of treatment.

11.7.3 Listing of Deaths, Other Serious and Clinically Meaningful Adverse Events

- A listing of all deaths, including site, number of instillations received, cause of death, autopsy, circumstances description, whether associated with an AE, if yes what AE, time from start of first exposure and time from last exposure

11.7.4 Other Safety Data

All analyses (not including shift tables) specified below will be done separately for

a) Baseline, Main treatment period of 6 instillation, Lab 1 and Lab 2 visits (for CBC, renal and liver function tests), the PDE visit and re-evaluation visits if relevant.
b) All the remaining visits (Maintenance and follow-up visits)

11.7.4.1 Laboratory Results

Hematology - Complete Blood Count

- Descriptive statistics of hematology results, including change from baseline, by visit.
- Frequency distribution of hematology results (within normal range / not clinically significant / clinically significant) by test and visit.
- Toxicity score shift table for key hematologic parameters from Baseline to the worst post-baseline result. The results will be coded based on CTCAE V5.0 into Grade 0 to Grade 4.
    (1) From Baseline to PDE visit.
    (2) From Baseline to the worst condition observed during the treatment period.
    (3) From Baseline to Study Completion visit

Renal and Liver Function

- Descriptive statistics of renal and liver function results, including change from baseline, by visit.
- Descriptive statistics for creatinine and eGFR by visit for patients with Renal Urinary AESIs.

- Descriptive statistics for creatinine and eGFR Tests before and after onset of Urinary Obstruction adverse events with no documented resolution or resolved with sequelae.
- Frequency distribution of results (within normal range / not clinically significant / clinically significant) by test and visit.
- Frequency distribution of creatinine and eGFR by visit for patients with Renal Urinary AESIs.
- Frequency distribution of creatinine and eGFR by visit for patients with single kidney.
- Toxicity score shift table for key renal and liver test from Baseline to the worst post-baseline result. The results will be coded based on CTCAE V5.0 into Grade 0 to Grade 4.
    (1) From Baseline to PDE visit.
    (2) From Baseline to the worst condition obtained during the treatment period.
    (3) From Baseline to Study Completion visit
- Toxicity grade shift from baseline to PDE visit for creatinine and eGFR for patients with Renal Urinary AESIs.
- Toxicity grade shift from baseline to the worst value obtained during the treatment period for creatinine and eGFR for patients with Renal Urinary AESIs.
- Toxicity grade shift from baseline to study completion visit for creatinine and eGFR for patients with Renal Urinary AESIs.
- Spaghetti plots for eGFR (one line per patient)

Coagulation Tests

- Descriptive statistics of coagulation test results, including change from baseline, by visit.
- Frequency distribution of results (within normal range / not clinically significant / clinically significant) by test and visit

Urinalysis/ Dipstick

- Descriptive statistics of numeric results (pH and specific gravity only), including change from baseline, by visit.

- Frequency distribution of Normal (Negative) / Abnormal (Positive) not clinically significant / (Positive) Abnormal Clinically Significant results by test and visit

  If normal ranges are applicable, the frequencies will be provided by clinically significant within normal range / not clinically significant / clinically significant
- By-patient listing of urinalysis parameter results, including visit, normal / abnormal (including clinical significance)

Urine Culture

- Frequency distribution of urine culture result by visit

Potentially Clinically Significant (PCS) Results

- Frequency of patients meeting criteria for potentially clinically significant (PCS) results, defined as follows:

Lab Parameter	Conventional Unit	Lower Limit	Upper Limit
Biochemistry			
Creatinine	mg/dL		> 2.2
ALT	U/L		> 3 x upper limit of normal
AST	U/L		> 3 x upper limit of normal
Total Bilirubin	mg/dL		> 1.5 x upper limit of normal
Gamma glutamyl-transferase	U/L		> 2.5 x upper limit of normal
INR	ratio		> 1.5
Potassium	mEq/L	< 3.0	> 5.5
Sodium	mEq/L	≤ 130	> 150
Hematology			
Hemoglobin	g/dL	<0.8 x lower limit of normal and >20% decrease from baseline	>1.3 x upper limit of normal and >30% increase from baseline
Leukocytes	$x10^3/\mu L$	≤ 2.8	≥ 16.0
Lymphocytes	$x10^3/\mu L$	< 0.5	> 20
Neutrophils	$x10^3/\mu L$	< 1.0	
Platelets	$x10^3/\mu L$	< 75	≥ 700

- Abnormal Liver Function Test Results: Frequency of patients meeting the criteria for abnormal liver function tests (LFTs) at any time post-baseline by treatment group according to the following criteria:
  - ALT > 3 x upper limit of normal

- ALT > 5 x upper limit of normal
- ALT > 10 x upper limit of normal
- AST > 3 x upper limit of normal
- AST > 5 x upper limit of normal
- AST > 10 x upper limit of normal
- ALT OR AST > 3 x upper limit of normal AND Total bilirubin > 2 x upper limit of normal without findings of cholestasis (i.e. serum alkaline phosphatase activity less than 2× the upper limit of normal)

11.7.4.2 Vital Signs

- Frequency distribution of the following heart rate (HR, bpm) results, by visit and overall

  (1) High
  - if HR ≥ 120 bpm
  - if HR ≥ 120 bpm or there was an increase of at least 15 points on HR from baseline

  (2) Low
  - if HR ≤ 50 bpm
  - if HR ≤ 50 bpm or there was a reduction of at least 15 points on HR from baseline

  The "total" will present any post-baseline visit.
- Frequency distribution of the following systolic blood pressure (SBP, mmHg) results, by visit and overall

  (1) High
  - if SBP ≥ 180 mmHg
  - if SBP ≥ 180 mmHg or there was an increase of at least 20 points on SBP from baseline

  (2) Low
  - if SBP < 90 mmHg
  - if SBP < 90 mmHg or there was a reduction of at least 20 points on SBP from baseline

  The "total" will present any post-baseline visit.
- Frequency distribution of the following diastolic blood pressure (DBP, mmHg) results, by visit and overall

(1) High
- if DBP ≥ 105 mmHg
- if DBP ≥ 105 mmHg or there was an increase of at least 15 points on DBP from baseline

(2) Low
- if DBP < 50 mmHg
- if DBP < 50 mmHg or there was a reduction of at least 15 points on DBP from baseline

The "total" will present any post-baseline visit.

- By-patient listing of all vital signs results, by visit
- By-patient listing of clinically significant abnormal vital signs results, by visit

11.7.4.3 Physical and Urology Oriented Examination

General Physical Examination

- By-patient listing of all general physical examinations results, by visit
- By-patient listing of clinically significant abnormal physical examinations results, by visit

11.7.4.4 Urology Oriented Examination

- By-patient listing of all urology oriented examination results, by visit
- By-patient listing of clinically significant abnormal urology oriented examination results, by visit

11.7.4.5 Post-Treatment Urination

Descriptive statistics by instillation for the following

- Time to first urination and to first clear urination post treatment (no purple color), as collected after each Treatment during the Telephone Contact

11.7.4.6 Pain during Instillation

- Descriptive statistics of degree of pain, VAS, experienced by patients during the instillation, by visit

11.7.4.7 CTU/MRI

- Summary of CTU/MRI results at screening and study completion
- By-patient listing of CTU/MRI results

11.8 PK Analysis

PK analysis will be performed using the PK analysis set.
Actual blood sampling times will be used in all PK analyses. Per protocol times will be used to calculate mean plasma concentrations for tabular and graphical displays. Spaghetti graphs of plasma concentrations and average over all patients will be presented on original and semi-logarithmic scale.

Pharmacokinetic parameters for MMC will be calculated using non-compartmental analysis (directly from the by-patient profile). Only plasma concentrations equal to or greater than the validated lower limit (LOQ) of the assay will be used in the PK analysis. For the PK analysis, plasma concentrations < LOQ that occur from pre-dose to the first concentration ≥ LOQ will be taken as 0 and those that occur thereafter will be taken as missing.
The elimination rate constant, λz, will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The slope will be determined from a plot of the natural log of the terminal plasma concentrations against time; at least 3 terminal plasma concentration time points, beginning with the final concentration ≥ LOQ and not including Cmax, will be selected for the determination of λz; the regression will have $R^2 \geq 0.90$.

- Descriptive statistics of plasma concentration by time will be presented.
- Descriptive statistics of PK parameters will be presented.
- Spaghetti graphs of plasma concentrations and average over all patients will be presented on original and semi-logarithmic scale.

12 Data Listings

Data listings will be provided for all data available from the CRF.

13 Computer Software

All statistical analyses will be carried out using SAS® Version 9.4 or higher under Windows® 2016 Terminal.

14 Change in the Planned Analysis from Protocol

The following changes from the protocol have been made in this statistical analysis plan, organized according to the section numbering of the protocol:

Protocol Section18 Statistical Methodology:

- Protocol Section 18 includes hierarchical testing of hypotheses. This approach was revised and it is not included in the SAP.
- The protocol proposed to "avoid operational bias by providing the access to cumulative ongoing trial data to an independent body only." In practice this did not occur.

18.4 Analysis Sets:

- Local Modified Intent-to-Treat (mITT) analysis set defined in the protocol was renamed as mITT analysis set in SAP and there is no reference in mITT analysis set definition to 'confirmed LG UTUC at Screening.'

18.4.4 Per Protocol (PP) analysis set 1 was defined in the SAP as a subset of the mITT analysis set in SAP while in the Protocol it was defined as a subset of the local mITT analysis set.

18.4.5 Per Protocol (PP) analysis set 2 was defined as a subset of the PP1 analysis set in SAP while in the protocol it was defined as a subset of the local mITT analysis set.

18.4.6 PDE_{CR} analysis population definition was updated to exclude patients with UUT Cytology = 'Suspicious for High Grade Urothelial Carcinoma' at PDE visit from both local and central labs

18.6 Demographic and Baseline Characteristics: Analysis set was changed from Safety to ITT.

18.7.1 Primary Efficacy Analyses: 'Necessary follow-up' was renamed as 'repeated evaluation' in SAP in accordance with CRF.

18.7.2 Sensitivity Analysis for the Principal Analysis of the Primary Endpoint: Local diagnosis was changed from local mITT analysis set (Protocol) to mITT analysis set (SAP).

18.8.1 Adverse Events: Breakdown of AEs and SAEs by volume of instillation were proposed in the protocol but not included in the final SAP.

18.8.2 Safety Laboratory Tests: Protocol included individual patients' listings of PCS measurements which are not included in SAP.

18.8.5 Tolerability Assessments: The protocol proposed: '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.' This analysis is not included in the SAP.

18.8.6 Use of Concomitant Medications:

- Pre and post instillation concomitant medications changed to related and not related to urothelial carcinoma concomitant medications in SAP
- Prohibited Medications summary is not included in SAP

15 Amendment 1 - Summary of Changes

Section	Revisions
7.3.2.4	A table summarizing censoring rule was included. Time-to-recurrence derivation formula was included. The rule for the start day of time to recurrence is added. A new rule for PDE_{CR} exclusion based on UUT local and central labs was added.
8.3	Added for CR=Failure based on UUT Local and Central Lab
8.4	'Indeterminate response' is added in the following statement: *If "Complete Response Durability Assessment" at any follow-up visit is marked as "Durable complete response at target area," all previous follow-up visits with missing assessment of durability of CR or indeterminate response are defined as CR ("Success"/no recurrence.* Revised text for duration of response continuous endpoint: "*The analysis for this endpoint will serve as the primary analysis to assess and describe the long-term durability endpoint."* Revised text for duration of response dichotomous endpoint: "*The analysis for this endpoint will serve as a supportive approach to describe the long-term durability endpoint, but will be the endpoint considered for the hypothesis testing for the key secondary endpoint as defined in the protocol*." The paragraph describing censoring rules was removed as the rules were included in Section 7.3.2.4
10	The statement regarding no interim analysis is planned was removed and statements about analyses for the interim clinical study report based on an early data cut-off was added.
11.2	The definition for the number of past episodes derivation was clarified.

Section	Revisions
11.4	Added reporting requirement for number and percentage of patients for whom general anesthesia was given, out of patients receiving treatment any time during treatment and maintenance periods.
11.5.3	Key secondary endpoint definitions and planned analyses were clarified to indicate the hypothesis testing will be performed using the dichotomous endpoint using exact binomial test. Results for key secondary dichotomous endpoints are to be presented as frequency distribution of dichotomous observed long-term durability of CR, along with a two-sided 95% exact binomial confidence interval. Additional analyses for duration for study follow-up and duration of follow-up post CR. Added clarification: the standard error and 95% confidence interval of the estimate will be calculated using Greenwood's method. Added requirement for reporting: • summary of events and censoring • time (months) to recurrence computed as [Recurrence date – CR response date + 1]/30.4375 • duration of follow-up post PDE visit computed as [End of study date – CR response date + 1]/30.4375 • duration of study follow-up computed as [End of study date – first dose date + 1]/30.4375.
11.5.4	Rules for selection of the observed results from central laboratory based on availability of local labs results were added. The following analysis was removed: "*Based on the Kaplan-Meier curve, the recurrence-free rates at 3, 6, 9 months post PDE will be estimated along with the 95% confidence intervals.*"

Section	Revisions
11.5.6	Included clarification: no p-values will be reported for subgroup analyses. Added requirement to present subgroup analyses results using forest plots. Subgroup analyses for continuous secondary endpoint using Kaplan-Meier analysis were removed.
11.5.7.1	Included clarification: no p-values will be reported. Added requirement to present results using forest plot.
11.5.7.3	Clarified this sensitivity analysis may be performed based on observed results.
11.7.2	Added data handling rules for partial AE start/stop dates Removed references to adverse events leading to study discontinuation as data was not collected in the CRF. Added summary of adverse events for all grades and grade 3/4 and summary of adverse events reported in >=10% (any grade) or >=5% (grade 3/4) of patients. AESI: Added summary of duration of stent for patients with adverse events of Urinary Tract Obstruction and summary for number of instillations prior to onset of urinary obstruction adverse events with no documented resolution or resolved with sequelae.

Section	Revisions
11.7.4.1	Added analyses: • Descriptive statistics for creatinine and eGFR by visit for patients with Renal Urinary AESIs. • Descriptive statistics for creatinine and eGFR by visit for patients with single kidney. • Descriptive statistics for creatinine and eGFR Tests before and after onset of Urinary Obstruction adverse events with no documented resolution or resolved with sequelae. • Frequency distribution of creatinine and eGFR by visit for patients with Renal Urinary AESIs. • Frequency distribution of creatinine and eGFR by visit for patients with single kidney. • Toxicity grade shift from baseline to PDE visit for creatinine and eGFR for patients with Renal Urinary AESIs. • Toxicity grade shift from baseline to the worst value obtained during the treatment period for creatinine and eGFR for patients with Renal Urinary AESIs. • Toxicity grade shift from baseline to study completion visit for creatinine and eGFR for patients with Renal Urinary AESIs.
14	Administrative changes.