

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211728Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

**New Drug Application (NDA)/Biologics License Application (BLA)
Multi-Disciplinary Review and Evaluation**

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the Food and Drug Administration (FDA).

Application Type	NDA
Application Number(s)	211728
Priority or Standard	Priority
Submit Date(s)	October 18, 2019
Received Date(s)	October 18, 2019
PDUFA Goal Date	April 18, 2020
Division/Office	DO1/OOD/OND/CDER
Review Completion Date	April 14, 2020
Established Name	Mitomycin gel
(Proposed) Trade Name	JELMYTO
Pharmacologic Class	Alkylating drug
Code name	UGN-101
Applicant	UroGen Pharma, Inc.
Formulation(s)	Gel
Dosing Regimen	Instill 4 mg per mL (not to exceed 15 mL) once weekly for six weeks. For patients with CR 3 months after JELMYTO initiation, may be administered once a month for maximum of 11 additional instillations
Applicant Proposed Indication(s)/Population(s)	Treatment of low-grade Upper-Tract Urothelial Cancer
Recommendation on Regulatory Action	Priority Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of low-grade Upper-Tract Urothelial Cancer

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Reviewers of Multi-Disciplinary Review and Evaluation

[FDA will complete this section.]

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DEPI = Division of Epidemiology; DHOT = Division of Hematology Oncology Toxicology; DMEPA = Division of Medication Error Prevention and Analysis; DRISK = Division of Risk Management OB = Office of Bioequivalence; OCP = Office of Clinical Pharmacology; OHOP = Office of Hematology and Oncology Products; OPDP = Office of Prescription Drug Promotion; OPQ = Office of Pharmaceutical Quality; OSI = Office of Scientific Investigations; OSE = Office of Surveillance and Epidemiology.

Glossary

AE	adverse event
ADME	absorption, distribution, metabolism, excretion
AESI	adverse event of special interest
ANDA	Abbreviated New Drug Application
APTT	Activated Partial Thromboplastin Time
AUC	area under the plasma concentration-time curve
AUC ₍₀₋₆₎	area under the plasma concentration-time curve from 0 to 6 hours
AUC _{inf}	area under the plasma concentration-time curve from 0 to extrapolated infinity
BCG	Bacille Calmette Guérin
BLA	Biologics License Application
BMI	body mass index
BTD	Breakthrough Therapy Designation
CFR	Code of Federal Regulations
CKD	chronic kidney disease
C _{max}	highest concentration achieved in plasma
CMC	chemistry, manufacturing, and controls
COA	Clinical Outcome Assessment
CR	complete response
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CVA	cerebrovascular accident
DEPI	Division of Epidemiology
DHOT	Division of Hematology Oncology Toxicology
DILI	drug-induced liver injury
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
DRISK	Division of Risk Management
EC	Ethics Committee
ECG	electrocardiogram
FDA	Food and Drug Administration
FU	follow up
GCP	good clinical practice
GFR	glomerular filtration rate
GLP	good laboratory practice
HG	high grade
ICF	informed consent form

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IND	Investigational New Drug
IRB	Institutional Review Board
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ITT	intent to treat
K ₂ EDTA	dipotassium ethylenediaminetetraacetic acid
LG	low grade
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle-invasive bladder cancer
mITT	modified intent to treat
MP	maintenance period
NA	not applicable
NCR	no complete response, non-complete response
NDA	New Drug Application
NDD	no detectable disease
NME	new molecular entity
NMIBC	non-muscle invasive bladder cancer
NOAEL	no-observed-adverse-effect level
NR	no response
OB	Office of Bioequivalence
OCp	Office of Clinical Pharmacology
OHOP	Office of Hematology and Oncology Products
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigations
PDE	Primary Disease Evaluation
PDE _{CR}	complete responders at the PDE visit
PK	pharmacokinetics
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	preferred term
RC	radical cystectomy
REMS	risk evaluation and mitigation strategy
RLD	referenced listed drug
RNU	radical nephroureterectomy
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety

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SOC	system organ class
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life
TEAE	treatment -emergent adverse event
T_{last}	last sampling time when mitomycin concentrations were quantifiable
T_{max}	time to highest plasma concentration
TP	treatment period
TURBT	transurethral resection of bladder tumor
UC	urothelial cancer
UGN-101	mitomycin gel for urothelial instillation (formerly known as MitoGel)
UGN-102	mitomycin gel for urinary bladder instillation (formerly known as VesiGel)
UPJ	ureteropelvic junction
URS	ureterorenoscopy
USPI	United States Prescribing Information
US	United States
UTI	urinary tract infection
UTUC	Upper Tract Urothelial Carcinoma
UUT	upper urinary tract
WRO	Written Response Only
λ_z	elimination rate constant

1 Executive Summary

1.1. Product Introduction

UGN-101 consists of mitomycin, an alkylating drug, in combination with a sterile hydrogen that is liquid at 2-8°C but is a semisolid gel at room temperature. UGN-101 has a concentration of 4 mg per mL of mitomycin.

UGN-101 is a new medical entity and is not currently indicated for the treatment of any disease.

The applicant proposed the following indication:

JELMYTO is an alkylating drug indicated for the treatment of low-grade Upper Tract Urothelial Cancer (UTUC).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Low-grade upper tract urothelial carcinoma (LG-UTUC) occurs in the upper urinary tract, encompassing the renal calyces and pelvis and ureters. While LG-UTUC is associated with a low risk of progression to metastatic disease, local progression may result in kidney and/or ureter obstruction, bleeding, and infection. Conservative management with endoscopic resection or ablation is possible in a subset of low-risk patients with accessible tumors. However, for patients with recurrent disease or those not amenable to ablation, the standard of care is radical nephroureterectomy (RNU), which is associated with a 15% incidence of post-operative morbidity and a 90-day mortality rate of approximately 4-5%. Currently, there are no FDA-approved therapies for patients with LG-UTUC.

OLYMPUS (UT001) was conducted by UroGen and submitted as the key trial in this application. OLYMPUS was an ongoing, single-arm trial that enrolled patients with non-invasive LG-UTUC who were either treatment-naïve or had recurrent disease and had at least one measurable papillary tumor 5-15 mm located above the ureteropelvic junction. Debulking was allowed prior to trial entry.

Patients were treated with UGN-101 4 mg per mL with total instillation volume based on individualized volumetric measurements using pyelography with the intent to fill the renal pelvis. Patients received six instillations once a week during the treatment period and tumor response was then evaluated at the Primary Disease Evaluation (PDE) visit which occurred five weeks after the last instillation. The primary efficacy outcome was CR rate at the PDE visit. CR was determined based on the absence of disease based on visualization, biopsy (if warranted), and cytology. Central pathology review was performed, however local laboratory results were used to define response. Clear definition of a negative cytology result was not provided in the protocol or statistical analysis plan (SAP). For patients with an equivocal

cytology result at the PDE visit, a negative result on follow-up was required for a CR. Patients who demonstrated complete response (CR) were allowed to enter a maintenance period in which they received up to 11 additional instillations once per month. Patients underwent subsequent follow-ups using the same methods of assessment at months 3, 6, 9, and 12 following the PDE visit. Duration of response, calculated as the time from demonstration of response, was a secondary endpoint.

A total of 71 patients were treated with UGN-101 on OLYMPUS, of whom 48% had tumors in locations not amenable to endoscopic resection per the investigator and 48% had tumors that had recurred after prior endoscopic therapy. Given the lack of detailed pre-specification of what constituted a positive local cytology result, FDA carefully reviewed both the local laboratory and central pathology results to ensure that patients with cytology suspicious for persistent or recurrent disease were not considered to have achieved or remained in CR. Based on this review, FDA determined that 41 patients (58%; 95% CI: 45%, 69%) had a CR at the first disease assessment. Duration of response ranged from 0 to 18.8 months. The median duration of response was not reached as of the data cut-off. Nineteen patients (46%) achieved a CR that persisted at the 12-month visit following the PDE. The duration of response data were immature at the time of data cut-off with 11 patients continuing to be followed for duration of response without recurrence, including 9 who had either not yet reached the 12-month visit or were considered indeterminate for ongoing response at that visit.

The most common (>20%) adverse events in OLYMPUS included ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting. Forty-two percent of patients experienced Grade 3-4 AEs, the most common (>2%) of which included ureteric obstruction, urinary tract infection, vomiting, flank pain, renal dysfunction, and dysuria. UGN-101 was discontinued due to an adverse event in 21% of patients, most commonly due to ureteric obstruction. Ureteric obstruction was reported in 58% of patients, necessitating intervention in the majority of these patients including ureteral stent placement, balloon dilatation, and rarely nephroureterectomy. Two patients experienced Grade 3 thrombocytopenia and/or neutropenia. While no gross extravasation of UGN-101 was noted in these patients, systemic exposure to mitomycin leading to cytopenias could not be ruled out. Two patients died due to adverse events during the study, one due to stroke which was assessed as unlikely to be related to the study drug, and one due to 'failure to thrive,' which was assessed by the FDA as due to a urinary tract infection that may have been study drug-related.

The review team recommends that UGN-101 receive regular approval for the proposed indication based on the results of OLYMPUS. This conclusion is based on demonstration of a complete response rate and durability that provide meaningful clinical benefit to patients with LG UTUC that may delay or preclude the need for nephroureterectomy, a surgical procedure with high rates of morbidity and mortality. Although the protocol did not adequately

prespecify interpretation of cytology results in the definition of complete response, FDA review of both the local and central laboratory results lead to a change in complete response status in only two patients. The safety profile of UGN-101 was acceptable, particularly in the context of potential nephroureterectomy as the alternative therapy. Ureteric obstruction was common but was manageable with local interventions and did not commonly result in severe renal dysfunction. The review team believes that the magnitude of the observed CR rate and duration provides a benefit that outweighs the risks associated with UGN-101. A post-marketing commitment based on the final trial results to better characterize the response duration, risk for progression, and need for subsequent nephroureterectomy was agreed upon with the applicant.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Low-grade upper tract urothelial carcinoma (LG-UTUC) is associated with frequent recurrence and local progression that may result in kidney and/or ureter obstruction, bleeding, and infection. Conservative management with endoscopic resection or ablation is possible in a subset of low-risk patients with accessible tumors. However, for patients with recurrent disease or those not amenable to ablation, the standard of care is radical nephroureterectomy (RNU), which is associated with a 15% incidence of post-operative morbidity and a 90-day mortality rate of approximately 4-5%. Currently, there are no FDA-approved therapies for patients with LG-UTUC.

OLYMPUS (UT001) was an ongoing, single-arm trial that enrolled patients with LG-UTUC who were either treatment-naïve or had recurrent disease and had at least one measurable papillary tumor 5-15 mm located above the ureteropelvic junction. Patients were treated with UGN-101 4 mg per mL with total instillation volume based on individualized volumetric measurements using pyelography with the intent to fill the renal pelvis. Patients received six instillations once a week during the treatment period and tumor response was then evaluated at the Primary Disease Evaluation (PDE) visit which occurred five weeks after the last instillation. The primary efficacy outcome was CR rate at the PDE visit. CR was determined based on the absence of disease based on visualization, biopsy (if warranted), and cytology. Central pathology review was performed, however local laboratory results were used to define response. Duration of response, calculated as the time from demonstration of response, was a secondary endpoint. The FDA considered responses lasting at least 12 months from initial response to be a clinically meaningful duration.

Of 71 patients treated with UGN-101 on OLYMPUS, 41 patients (58%; 95% CI: 45%, 69%) had a CR at the PDE visit. Duration of response ranged from 0 to 18.8 months. The median duration of response was not reached as of the data cut-off. Nineteen patients (46%) achieved a CR that persisted at the 12-month visit following the PDE. The duration of response data were immature at the time of data cut-off with 11 patients continuing to be followed for duration of response without recurrence, including 9 who had either not yet reached the 12-month visit or were considered indeterminate for ongoing response at that visit.

The safety profile of UGN-101 was considered acceptable compared to nephroureterectomy. The most common (>20%) adverse events in OLYMPUS included ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting. Ureteric obstruction was reported in 58% of patients, including 19% with Grade 3 events, necessitating intervention in the majority of these patients that included ureteral stent placement, balloon dilatation, and rarely nephroureterectomy. Two patients experienced Grade 3 thrombocytopenia and/or neutropenia, which did not appear related to systemic exposure via gross extravasation of UGN-101. One patient died due to stroke; this death was assessed as unlikely to be related to the study drug.

The review team concludes that UGN-101 has a favorable risk-benefit profile for the treatment of LG-UTUC and recommends regular approval of this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	Patients with LG UTUC experience frequent local recurrence and are at risk for ureteric obstruction, infection, and bleeding.	LG UTUC represents a serious condition given risk for local complications.
<u>Current Treatment Options</u>	- Endoscopic resection is recommended as conservative management of LG UTUC, but many patients may not be candidates due to multi-focality, recurrent disease, tumor size, and/or location. - Nephroureterectomy is the standard of care for LG UTUC that cannot be managed via endoscopic interventions	There are no non-surgical options available for LG-UTUC not amenable to endoscopic interventions. Nephroureterectomy may be curative, however is associated with high rates of morbidity and mortality.
<u>Benefit</u>	- Complete response rate following UGN-101 was 58% (45%, 69%) 46% of responders remained in CR at the 12-month visit subsequent to CR determination. Median duration of response had not been reached as of the data cut-off.	The observed complete response rate and duration of complete response are clinically meaningful. The duration of follow-up remains insufficient to determine the median duration of

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- There were no events of progression to invasive or high-grade UTUC. - Interpretation of cytology for CR determination was inadequately defined in the protocol. Review of verbatim local and central pathology was performed and resulted in change of CR status and change in duration of CR in one patient each respectively.	response.
Risk and Risk Management	- The most common adverse events included ureteric obstruction, flank pain, urinary tract infection, hematuria, renal dysfunction, fatigue, nausea, abdominal pain, dysuria, and vomiting - Ureteric obstruction was common (58%) and commonly required interventions including ureteral stent placement. - Two patients experienced Grade 3 thrombocytopenia and/or neutropenia without observed gross extravasation - There were no deaths likely due to UGN-101 on study	The major toxicities of UGN-101 appeared related to repeated instrumentation of the upper tracts, including ureteral inflammation, stenosis, and infection. Resulting ureteric obstruction was common but appeared manageable with ureteral interventions and did not result in severe obstructive uropathy. A warning will be added both for ureteric obstruction and cytopenias related to UGN-101. The risks of UGN-101 appear acceptable given the observed efficacy of UGN-101 and alternative therapy of nephroureterectomy.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
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☐	Clinical outcome assessment (COA) data, such as	Not applicable
☐	Patient reported outcome (PRO)	
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (eg, individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	Not applicable
☐	Patient-focused drug development or other stakeholder meeting summary reports	Not applicable
☐	Observational survey studies designed to capture patient experience data	Not applicable
☐	Natural history studies	Not applicable
☐	Patient preference studies (eg, submitted studies or scientific publications)	Not applicable
☐	Other: (Please specify)	Not applicable
☐	Patient experience data that was not submitted in the application but was considered in this review.	

X

Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Upper Tract Urothelial Carcinoma (UTUC) is an epithelial malignancy that is histologically identical to urothelial bladder cancer and occurs in 2 histologic forms: high grade (HG) and low grade (LG). It is a rare disease with an incidence of 1 to 2 people per 100,000 Americans. Patients with LG UTUC are the intended population for treatment with mitomycin gel for urothelial instillation (UGN-101). LG UTUC most commonly presents in elderly people (average age at diagnosis: 74 years) who also suffer from comorbid conditions such as hypertension, diabetes, obesity and the metabolic syndrome ([Browne et al. 2018](#)) and is more common in males than females. LG UTUC typically presents with painless hematuria; diagnosis is made via visualization (ureteroscopy), biopsy of suspicious lesions, and cytology. Local laboratories typically provide the cytologic and histologic diagnoses.

Low grade cancer represents 40% of the total upper tract disease burden (incidence of ~3000 cases per year, with a prevalence ~15,000). If left untreated, the overall risk of progression for patients with LG papillary UTUC is estimated to be about 5%; however, the greatest risk to the LG UTUC patient is to the renal system because of disease spread within the lining of the upper urinary tract (UUT) to locations that are not amenable to conservative management, and thus require radical nephroureterectomy (RNU). Renal loss in this population is associated with a significant risk of renal insufficiency and renal failure. Other risks of LG UTUC are associated with kidney and/or ureter obstruction leading to impaired renal function and other effects of tumor overgrowth such as bleeding and infection due to friability of the tumor and pain.

The FDA's Assessment:

FDA agrees with the Applicant's position. Management guidelines for LG UTUC include conservative management, such as nephron-sparing endoscopic excision, for selected patients with low-risk disease, which may include unifocal disease and small tumor size (e.g. <1.5-2 cm). Patients with higher-risk features, such as hydronephrosis, large tumor size, high-grade histology/cytology, multifocality, are generally recommended to undergo radical nephroureterectomy (RNU). For patients with low-risk UTUC, no prospective randomized trials have been conducted to compare the outcome of endoscopic management vs RNU. LG UTUC rarely progresses to invasive disease (8-14%; Cutress et al BJU 2012), although the data regarding the natural history of LG UTUC is limited due to inconsistent reporting from different institutions and limitations of the diagnostic accuracy of ureteroscopic biopsy, and is generally associated with local tumor effects. Recurrence after endoscopic treatment is common (~30-50%; Cutress et al BJU 2012) and may be an indication for RNU.

2.2. Analysis of Current Treatment Options

No drug therapy has been approved by FDA for the treatment of LG UTUC in either an adjuvant or first-line use setting. Previously, administration of adjuvant topical chemo- and immunotherapy following endoscopic treatment has not demonstrated clear evidence of benefit, likely due to the short dwell time in the target organs due to normal urine flow and the absence of reservoir capacity ([Knoedler and Raman 2018](#); [Cutress et al. 2012a](#); [Cutress et al. 2012b](#)). Surgical intervention is the only treatment supported by established clinical practice or clinical guidelines, and includes removal of the kidney and ureter (i.e., RNU) and/or endoscopic therapy (i.e., ureteroscopy and laser ablation, or percutaneous resection) ([Browne et al. 2018](#); [Mandalapu et al. 2017](#); [Cutress et al. 2012b](#)).

The majority of patients with LG UTUC undergo RNU. Kidney and ureter removal is a first-line therapy for most patients and is employed in cases of large tumor volume or multifocality, endoscopically inaccessible tumor location (i.e., endoscopically unresectable tumors) or the failure of prior endoscopic surgery. Large cohort studies underscore the fact that most patients with urinary tract tumors, approximately 80%, eventually undergo kidney and ureter removal ([Browne et al. 2018](#); [Scotland et al. 2018](#); [Cutress et al. 2012a](#); [Kohut and Zhu 2012](#)). The adverse impact of kidney removal in this population is multifaceted. Short-term complications of the surgery occur in 30% to 50% of patients irrespective of whether it is performed using an open or minimally invasive approach ([Raman and Jafri 2016](#); [Lin et al. 2014](#)). A third of these complications are Grade 3 or 4 and include gastrointestinal toxicity, bleeding, infection, and injury to adjacent organs ([Lin et al. 2014](#)). Long-term complications, such as renal insufficiency (approximately 50%) and renal failure (8%), also occur in a proportion of the population undergoing kidney removal ([Lee et al. 2018](#); [Leppert et al. 2018](#); [Kaag et al. 2010](#)). In addition, for those patients with reduced glomerular filtration rates (GFRs), this added burden includes the expense of managing related adverse effects, including dialysis, possible kidney transplant, and the risk of chronic kidney disease (CKD)-related morbidity, along with a notable decline in healthcare-related quality of life ([Thomas et al. 2017](#); [Daratha et al. 2012](#); [Go et al. 2004](#)). The medical, social, and economic burden of CKD and renal failure in the United States (US) is well-described and significant. The annual mortality rate for patients on dialysis is 20%, and cardiac morbidity resulting from reduced renal function accounts for half of all deaths in patients with CKD ([Go et al. 2004](#)). Reduced GFR is associated with an increased risk of hospitalization, fatal cardiac events, and premature death; and has been found to be as significant a risk for disability adjusted life years as elevated total cholesterol in both developed and developing nations ([Thomas et al. 2017](#)).

Endoscopic therapy is used in approximately 10% to 30% of cases, typically for removal of small solitary tumors reachable by laser or in patients with existing renal insufficiency or a solitary kidney. Endoscopic tumor resection carries a potential risk of injury to the urinary tract, bleeding, and infection, and tertiary centers offering repetitive endoscopic intervention for select patients with LG disease have reported treatment related morbidity including ureteral

stricture (3% to 51%), perforation of the UUT (4% to 23%), and bleeding and infection ([Cutress et al. 2012a](#)). Endoscopic tumor resection is also associated with high rates of local disease recurrence (50% to 90%). While there is significant variability in methodology, patient populations, baseline disease characteristics, nature of follow up (FU), and data reported, the literature reflects a consistently high recurrence rate within months of last treatment with mean/median time to recurrence of < 1 year, centering around 6 to 9 months ([Scotland et al. 2018](#); [Suriano et al. 2014](#); [Cornu et al. 2010](#); [Milner et al. 2006](#); [Daneshmand et al 2003](#); [Elliott et al. 2001](#)). This results in the need for life-long invasive surveillance for recurrence which typically includes repetitive endoscopic evaluation of the ureter and kidney ([Scotland et al. 2018](#); [Cutress et al. 2012b](#)).

Both methods of surgical intervention also carry, to varying degrees, the immediate and long term risks of surgery and anesthesia in the elderly ([Raman and Jafri 2016](#)), which may contribute to short and long-term effects in elderly patients including post-operative delirium and cognitive decline ([Greaves et al. 2019](#); [Krause et al. 2019](#); [Steinmetz and Rasmussen 2018](#)), and the cost of surgery and recovery from post-operative complications in the target population ([Pak et al. 2009](#)).

Given the inherent risk associated with surgical interventions and organ loss, the inadequate durability associated with laser treatments, and the lack of any other approved drug therapy, there is a substantial unmet medical need for treatment options for patients with LG UTUC.

The FDA's Assessment:

FDA agrees with the Applicant's position. Patients with low-grade UTUC who are managed with endoscopic excision may develop local recurrence and eventually require RNU. Additionally, many patients with LG UTUC may not be candidates for endoscopic management due to multifocality or inaccessible tumors. Tumors in the renal pelvis may be accessed percutaneously, although this approach carries a potential risk of tumor seeding. Particularly in patients with solitary kidneys and/or impaired renal function, RNU may have risk of renal failure that may require dialysis or kidney transplant.

Antegrade instillation of bacillus Calmette-Guerin (BCG) vaccine or aqueous mitomycin C into the upper tract, each of which has demonstrated evidence of reduction of recurrence in patients with non-muscle invasive bladder cancer, is feasible after endoscopic resection, however data regarding activity in UTUC are limited. Durable complete response is considered to be a clinical endpoint that directly measures the clinical benefit of a drug in this setting, in which progression to invasive disease is uncommon, but recurrent endoscopic intervention under general anesthesia is currently the only alternative to radical surgery. Avoidance of RNU in patients with low-grade UTUC is considered a clinical benefit.

3 Regulatory Background

3.1. US Regulatory Actions and Marketing History

The Applicant's Position:

Investigational New Drug (IND) 121922 for UGN-101 was opened in the US on 06 Nov 2016 for the treatment of LG UTUC. Prior to opening the IND, the sponsor held a series of preIND meetings, summarized in Table 1, to obtain FDA feedback on the proposed development plan. UGN-101 is not currently registered or approved in the US or in any other country.

Table 1 Key FDA Interactions PreIND

Type of Meeting	Date	Purpose of Meeting
PreIND [Ref 3506859]	24 Apr 2014	Primarily discussed adequacy of a single arm study using CR in LG UTUC patients as the primary endpoint with a 15% CR considered clinically relevant. Durability of response required as part of study design. Additionally, discussed the design of the proposed general toxicity study and the adequacy of future and existing nonclinical data to support an IND. Obtained agreement on the use of the 505(b)(2) regulatory pathway.
PreIND [Ref 3778958]	01 Jun 2015	Discussed the adequacy of the proposed pivotal clinical study to support an NDA. Agreement was reached on the definition of complete response (CR; primary endpoint) and the FU schedule to determine the duration of response. Sample size calculation, interim analysis plan, and early stopping criteria were also discussed.
PreIND [Ref 3844788]	05 Nov 2015	Discussed the adequacy of the design of the pivotal Phase 3 clinical study revised based on prior FDA advice. FDA provided feedback on the use of maintenance treatment, use of biopsies at CR, and individualization of dose. Agreement was reached to FU patients for up to 1 year for durability and the FDA clarified that durability data from all patients was not required for submission of the NDA. As a result of this meeting, additional recommendations were implemented into the study design, including a 12-month FU for safety and durability of CR.

CR = complete response; FU = follow up; IND = investigational new drug; FDA = Food and Drug Administration; LG UTUC = low grade upper tract urothelial cancer; NDA = New Drug Application.

The FDA's Assessment:

FDA agrees with the Applicant's position. The FDA notes that, at the preIND meeting in June 2015, the FDA recommended a randomized trial in which patients would be randomized to receive UGN-101 or placebo at the time of definitive resection of LG UTUC and then followed for recurrence, although noted that a very high response rate supported by long-term data (e.g. 12 month follow-up) in a small number of patients in a single arm trial may be acceptable. With regards to the definition of CR, while the FDA agreed in principle that visualization, biopsy for a visualized lesion, and cytology should all show absence of disease for a patient to be considered in CR, specific detail regarding the use and interpretation of cytology was not discussed.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

UGN-101 was granted Orphan Drug Designation (Ref 14-4451), Fast Track Designation (Ref 4136862), and Breakthrough Therapy Designation (BTD; Ref 4340250). BTD was granted on the basis of early complete response (CR) and durability data from clinical trial UT001 included in this New Drug Application (NDA). The sponsor conducted 3 separate preNDA interactions (meetings and written response only [WRO]) with the agency as described in Table 2.

Table 2 Key FDA Interactions preNDA

Type of Interaction	Date	Purpose of Meeting
PreNDA CMC meeting [Ref 4257982]	08 May 2018	Discussed and gained agreement on the adequacy of the proposed CMC data to support an NDA. Specific discussions were held on product description, specifications, residual solvents, leachable data, bridging to the RLD, manufacture of hydrogel, stability data and the human factors study.
PreNDA WRO [Ref 4286763]	06 Jul 2018	Discussed and gained agreement on the adequacy of the nonclinical data on UGN-101 and its excipients to support an NDA. Additionally, agreement was reached on the submission of datasets for legacy clinical studies in bladder cancer.
PreNDA clinical meeting [Ref 4346887]	06 Nov 2018	Discussed and gained agreement on the adequacy of the proposed clinical data to support an NDA. Agreement reached on the submission of full data on the primary endpoint with an interim cut off of durability data defined as 75% of patients with 6 months FU. Additionally, agreement reached on a rolling submission, pooling strategy, the use of the SCS and SCE to fulfill the requirements of the ISS and ISE, and the use of the 120-day safety update.
CMC = chemistry, manufacturing, and controls; CR = complete response; FDA = Food and Drug Administration; FU = follow up; IND = investigational new drug; ISE = integrated summary of efficacy; ISS = integrated summary of safety; NDA = New Drug Application; SCE = summary of clinical efficacy; SCS = summary of clinical safety.		

The FDA's Assessment:

FDA agrees with the Applicant's position.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI selected three clinical investigators, Dr. Surena Matin (Site 21), Dr. Phillip Pierorazio (Site 11) and Dr. Ahmad Shabsigh (Site 16) for clinical inspection. Inspection of Drs. Matin and Pierorazio found no significant regulatory deficiencies. Inspection of Dr. Shabsigh, who enrolled four subjects into the study, identified three patients with urine cytology results that were thought not to be consistent with the definition of complete response described in the study protocol. A Form FDA-483 was issued to the investigator with the following two Observations. Information contained in the Observations is summarized as follows:

- 1) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation
- 2) An investigation was not conducted in accordance with the investigational plan

The Clinical Inspector had additional comments (see below). The clinical reviewers subsequently requested verbatim local and central laboratory results from all patients determined by the sponsor to be in complete response. See Section 8.2 for further discussion regarding interpretation of cytology results.

***Reviewer's Comments:** Determination of a CR using the absence of HGUC in urine cytology at the PDE visit was not described or found in the approved study protocol.*

As specified in the Background of this summary, the protocol stated: "If visual ureteroscopy assessment indicated no remaining tumors, the upper tract urine cytology had to be negative". This statement indicates that both HGUG and low-grade carcinoma should be considered in determination of a CR. This is also reflected by the study CRF, which included HGUG and low-grade urothelial carcinoma in the checklist for the PDE visit. Regarding the three questioned subjects, the upper tract urine cytology results, as listed in the above table, did not clearly show that their urine cytology at the PDE was negative, but rather were questionable or equivocal in that low-grade carcinoma could exist or could not be excluded in the specimens read by local pathologists. See additional Reviewer's Comments below regarding the reported data for these three subjects.

Reviewer's Comments: *Given that three of the four enrolled subjects at Dr. Shabsigh's site had discrepancies between source records and the submitted primary endpoint data, the DOI review team was notified of the inspection observations immediately upon feedback from the inspection. Relevant documents including the ureteroscopy and urine cytology reports were conveyed in the Week of 2/24/2020. With the evidence found in these documents as well as the Observations specified in the issued Form FDA 483, we recommended the review team to communicate with the Applicant and clarify whether the three subjects (as listed in the above table) had urine cytology results that clearly showed "negative for urothelial carcinoma" to support the reported CRs. OSI also suggested conducting additional analyses as needed to address the issue and/or to accurately reflect the efficacy of mitomycin gel in the intended patient population.*

As discussed above, OSI review of the Investigator's written response, received on 3/24/2020, found that the Investigator's stated criteria for defining a CR at the PDE were related to whether high-grade urothelial carcinoma was detected in the upper tract urine cytology besides the requirement of no remaining tumors per ureteroscopy assessment. This is not well consistent with the criteria described in the study protocol (see Reviewer's Comments above), representing a considerable protocol deviation or a change in determination of a CR and/or interpretation of the reported efficacy data. Whether the change in the criteria is clinically relevant and whether the CR data from the three subjects from this study site is acceptable should be prudently assessed by the DOI review team.

4.2. Product Quality

The CMC review team from the Office of Pharmaceutical Quality recommends approval for the NDA. The Mitomycin for Solution component of UGN-101, intended to be reconstituted with hydrogel, had a ^{(b) (4)} proposed assay acceptance criterion (^{(b) (4)}%) than commonly used for pharmaceutical products (^{(b) (6)}%). This was determined to be acceptable since it is the same as that of the USP monograph and the listed drug. The applicant did not provide 12 months of stability data for eth registration batches, however the submitted 6-month registration stability data was deemed adequate to support the proposed expiry of 24 months shelf life when stored under long term conditions. The applicant will put the first three production scale lots of mitomycin for solution drug product on a stability program to confirm the granted expiry. Batch release and stability data of the hydrogel component supported the 24-month expiry date.

The UGN-101 admixture dissolution was found to be out of specification, potentially due to the

heterogeneity of the admixture and the sampling method. In discussion with the clinical review team, this was found to be acceptable given the dose (by volume), route of administration, and risk/benefit profile and the assay acceptance limit was changed to (b) (6)%, which is (b) (4) than the commonly used assay limit of (b) (6)%. (b) (6) considered acceptable.

4.3. Clinical Microbiology

The application was reviewed for sterility assurance for the hydrogel and mitomycin components separately and each was found to be adequate.

4.4. Devices and Companion Diagnostic Issues

The Applicant initially proposed (b) (4) devices used to prepare and administer UGN-101 as a kit, however later opted to describe the FDA-cleared or exempt devices, which include syringes, needles, closed system transfer devices, and Luer Lock connectors. The Applicant proposes a co-packaged kit as a supplemental submission. that CDRH was consulted to review two devices that were specified: the Uroject12 Syringe level and the UroGen Pharma chilling block to be used with the product. Per the CDRH reviewer, the Applicant adequately addressed all concerns regarding the use and labeling of both devices for the preparation and administration of UGN-101.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

FDA's Assessment:

Jelmyto (UGN-101, mitomycin gel for instillation, 0.4% [mg/mL]) is an admixture formulation of mitomycin (mitomycin-C, MMC) in sterile hydrogel. Hydrogel ((b) (4) sterile hydrogel) contains a (b) (4) Poloxamer (b) (4) and has high viscosity at body temperature and low viscosity (liquid-like) at refrigerated temperature. This temperature-dependent viscosity characteristic of hydrogel allows reconstitution of mitomycin with sterile hydrogel prior to administration and instillation of the cooled mitomycin gel into the upper urinary tract. After administration, mitomycin gel solidifies (semi-solid) at body temperature to form a drug reservoir which allows for extended exposure of mitomycin to the target organs/tissues. Mitomycin gel is intended to treat low-grade upper tract (b) (4) urothelial carcinoma (LG-UTUC, also known as upper urinary tract transitional cell carcinoma). A dose of 60 mg mitomycin gel (4 mg/mL) is administered locally into the upper urinary tract of patients with LG-UTUC once weekly for 6 weeks. For patients with a complete response, initial treatment is followed by maintenance therapy once monthly for up to 11 additional administrations.

UroGen Pharma Ltd. (UroGen, the Applicant, formerly TheraCoat) submitted a new drug application (NDA) for mitomycin gel for the treatment of patients with LG-UTUC under the 505(b)(2) pathway. The Applicant relied on FDA's previous findings of safety and effectiveness for the listed drug, Mutamycin (NDA 050450 discontinued) and FDA-approved labeling of Mitomycin for Injection (ANDA 064144). In addition, the Applicant submitted results from nonclinical pharmacology and intravesical repeat-dose toxicology studies conducted with mitomycin gel.

To support proof of concept, the Applicant conducted an in vivo pharmacology study of mitomycin in rats bearing bladder tumors. Rats received intravesical administration of 0, 0.5, 1, and 2 mg/dose mitomycin in hydrogel or 0.5 and 1 mg mitomycin in water for injection (MMC-WFI) on Days 5, 8, and 11. At the end of study, all rats in the untreated control group had tumors whereas 6 of 8 rats receiving 2 mg mitomycin gel were tumor free. No tumors were observed in rats receiving doses of 0.5 and 1 mg mitomycin gel. Instillation of 0.5 and 1 mg MMC-WFI inhibited tumor growth in 6 of 8 rats and 7 of 8 rats, respectively. Early mortalities occurred in rats treated with 1 and 2 mg mitomycin gel on Days 10-13. In general, drug-related clinical signs of toxicity, changes in body weight, and hematology parameters had higher frequency, severity, or both in the mitomycin gel groups than in the MMC-WFI groups. All mitomycin-treated rats had reduced body weights compared to controls, and urethral edema was noted after prolonged mitomycin exposure.

In nonclinical pharmacokinetic studies, intravesical administration of mitomycin gel in pigs resulted in low systemic exposure. In general, systemic exposure increased in a dose proportional manner with increasing dose. When compared to mitomycin solution, instillation of mitomycin gel achieved up to 13-fold higher concentrations in urothelial tissue, 6 hours after treatment.

The Applicant conducted a GLP repeat-dose retrograde instillation toxicology study of mitomycin gel in female pigs administered weekly for 6 weeks with a 4-week recovery. Doses up to 56 mg mitomycin gel (8 mg/mL) were instilled into the left upper urinary tract of female pigs. Partially recovered microscopic findings in the urinary system included edema, erosion, hypertrophy, and vacuolation of the urothelium with hemorrhage and leukocyte infiltration in the submucosa in the left kidney and ureter. Less frequent and severe microscopic findings were also noted in the right kidney and ureter.

Fertility studies with mitomycin gel were not conducted or needed to support a marketing application in the proposed patient population. Based on findings in animal studies and mechanism of action, mitomycin gel can cause fetal harm when administered to a pregnant woman. For genotoxic drugs like mitomycin, the guidance for industry “Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations” advises that females of reproductive potential use effective contraception during treatment and for 6 months after the last dose of Jelmyto. Male patients with female partners of reproductive potential should use effective contraception during treatment and for 3 months following the last dose. Because of the potential for serious adverse reactions in a breastfed child, women should not breastfeed during treatment with Jelmyto and for at least 1 week after the last dose.

The nonclinical pharmacology and toxicology data support approval of Jelmyto for the proposed indication.

5.2. Referenced NDAs, BLAs, Drug Master Files

The Applicant’s Position:

The referenced listed drug (RLD) for this 505(b)(2) NDA is Mutamycin® (mitomycin for injection; NDA 050450), that was previously approved in the US. for the treatment of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents, and as palliative treatment when other modalities have failed. The original Mutamycin NDA was withdrawn, resubmitted, and approved (Abbreviated NDA [ANDA] 062336) consequent to a change of the site of manufacture, not for reasons of safety or efficacy (FDA 2002). Subsequently, ANDA 062336 was withdrawn by the manufacturer and the FDA has approved mitomycin for injection (ANDA 064144, multiple strength presentations, Accord Healthcare 2014), as the presently designated reference standard. Therefore, the FDA clarified that UroGen can use the ANDA 064144 labeling, given that the ANDA must have the

same labeling as the RLD. Currently, the mitomycin for injection label is the designated reference standard and is the best representation of the labeling of the innovator.

The FDA's Assessment:

FDA agrees with the Applicant relying on Mutamycin as the listed drug and labeling from ANDA 064144.

5.3. Pharmacology

The FDA's Assessment:

Primary pharmacology

In a non-GLP in vivo study of mitomycin (MMC), tumors were established in female Fisher 344 rats by instilling rat AY-27 urothelial cell carcinoma cells into the bladder on Day 0. Various dose levels of MMC (administered in 0.6 mL) formulated either in TC-3 gel (MMC-TC-3, at 0.5, 1, and 2 mg/dose) or in Water for Injection (MMC-WFI, at 0, 0.5 and 1 mg/dose) were administered intravesically to each of the 6 study groups on Days 5, 8, and 11 through retrograde instillation. All surviving rats were euthanized on Day 14. All 8 rats in the untreated control group had tumors whereas no tumors were reported in rats receiving 0.5 and 1 mg MMC-TC-3. A dose of 2 mg MMC-TC-3 inhibited tumor growth in 6 of 8 rats. For the MMC-WFI-treated groups, instillation of 0.5 and 1 mg MMC-WFI inhibited tumor growth in 6 of 8 rats and 7 of 8 rats, respectively. There were no significant differences in number of macroscopic tumor foci when comparing between MMC formulated in TC-3 hydrogel or formulated in WFI. Early mortalities occurred only in MMC-TC-3 groups on Days 10-13 (40% and 90% at 1 and 2 mg/dose, respectively). In general, drug-related clinical signs of toxicity, changes in body weight, and hematology parameters had higher frequency, severity, or both for MMC-TC-3 groups than in MMC-WFI groups. In all MMC-treated rats (where MMC formulated in WFI or in TC-3), a significantly lower group mean body weight was noted when compared to controls. Urethral edema was noted after prolonged MMC exposure. (Study TRC-MMC-TC3-01)

Secondary Pharmacology

The Applicant's Position:

Secondary effects of mitomycin are recognized from a mechanistic perspective and are well described and inclusive of, but not limited to the following:

- Photon-mediated cycloaddition or cycloreduction (planar ring activation) with opposing DNA strand interactions independent of direct DNA crosslinking (Deans and West 2011);
- Suppression of cellular RNA and protein synthesis (Accord Healthcare 2014);

- Modification of redox cycling, ribosomal RNA inhibition, and modulation of thioredoxin reductase activity (Paz et al. 2012);
- Ancillary toxicodynamic associations (thrombocytopenia and leukocytopenia, pneumonitis, cardiac failure, and hemolytic uremic syndrome) are also associated with mitomycin (Verweij and Pinedo, 1990).

The FDA's Assessment:

The applicant is relying on FDA's previous findings of safety for Mutamycin. The referenced publications were not reviewed or needed to support approval of Jelmyto.

Safety Pharmacology

The Applicant's Position:

The overall safety pharmacology for mitomycin is well described in the scientific literature and in association with the approved drug product (RLD), Mutamycin, and as referenced (Accord Healthcare 2014).

The FDA's Assessment:

FDA agrees with the Applicant relying on FDA's previous findings of safety for Mutamycin.

5.4. ADME/PK

Absorption: Study PC-R UTUC-PIG-005

Six Retrograde Instillations of TC-3 Gel Mixed with Mitomycin C to Pig's Renal Pelvis

The average C_{max} of the 3 instillations (1, 4, and 6) in an animal that was instilled bilaterally with 40 mg of mitomycin was 3-fold higher in comparison to the average C_{max} of the unilateral instillation of 20 mg total (15.1 ng/mL versus 4.3 ng/mL, respectively). The highest C_{max} obtained for a single instillation in this study was 27.1 ng/mL, and was considerably below the toxic plasma level of mitomycin (400 ng/mL) (Crooke et al. 1976). Mitomycin was present in the plasma for more than 6 hours with average AUC values of 25.3 and 9.3 ng·hour/mL for bilateral and unilateral instillations, respectively.

Distribution: Study TAS-4M-TR-A-133

Mitomycin C Concentration in Urothelial Tissue Following Intravesical Instillation of TC-3 + Mitomycin C in Pigs

Higher concentrations of mitomycin were found in the urothelial tissue when mitomycin gel was used in comparison to mitomycin in liquid, with average tissue concentrations of 541.4 ng/mL versus 48.7 ng/mL mitomycin, respectively (11-fold higher with the gel), 2 hours following treatment with 1 mg/mL mitomycin. Six hours following the treatment, the urothelial tissue concentrations were 306 ng/mL vs 23.4 ng/mL, respectively (13-fold higher with the gel). The urothelial concentration of mitomycin obtained following instillation of 2 mg/mL mitomycin in gel was 1.8 times higher than the 1 mg/mL mitomycin in gel at 2 hours.

Metabolism: Locally instilled mitomycin results in limited systemic availability. Once absorbed, metabolism of mitomycin would be as per the RLD, Mutamycin.
Excretion: Locally instilled mitomycin is primarily eliminated in the urine upon dissolution of the gel depot. Systemically available mitomycin would be excreted as per the RLD, Mutamycin.
Toxicokinetic Data from General Toxicology Study 2189-007 Six-Week Repeat- Dose Toxicology Study in Female Pigs Using 2, 4, and 8 mg/mL/instillation (corresponding to 14, 28, and 56 mg mitomycin, respectively)
Plasma mitomycin concentrations were below the limit of quantitation of 0.10 ng/mL in all pre-dose samples from the mitomycin gel-treated animals and from control animals. The variability of the mean plasma mitomycin concentrations was high. The T_{last} varied from 2-6 hours on Day 1 (first instillation) to 2 to 10 hours on Day 36 (sixth instillation). The T_{max} was generally 0.5 hour. The highest mean C_{max} was noted in the group treated with 56 mg and was 4.93 ng/mL on Day 1 and 5.12 ng/mL on Day 36. Systemic exposure (AUC) and C_{max} values of mitomycin increased with increasing dose in an approximately dose-proportional manner on Days 1 and 36. The AUC of mitomycin appeared to decrease following repeated administration of mitomycin at 14 mg but did not appear to change following repeated instillations at the 28 and 56 mg doses. Individual accumulation ratios ranged from 0.211 to 0.684, 0.537 to 3.19, and 0.236 to 3.21 at 14, 28, and 56 mg doses of mitomycin, respectively. AUC = area under the plasma concentration-time curve; C_{max} = highest concentration achieved in plasma; T_{last} = last sampling time when mitomycin concentrations were quantifiable; T_{max} = time to highest plasma concentration.

The Applicant's Position:

The pharmacokinetic information for mitomycin gel supports the increased local exposure of the urothelium following administration, while reducing systemic exposure relative to mitomycin administered as a solution or mitomycin administered via parenteral routes of administration ([Accord Healthcare 2014](#)). Toxicokinetic analysis confirmed low systemic exposure to mitomycin following repeated administration and no increase in accumulation, irrespective of the instilled mitomycin dose.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

5.5. Toxicology

5.5.1. General Toxicology

NDA 211728 Multi-disciplinary Review and Evaluation
UGN-101 (mitomycin gel) for instillation

Study Title/Number: MITOGEL™: A Toxicologic Study of Repeated Retrograde Instillations to the Upper Urinary Tract in Swine/Study 2189-007

Key Study Findings

- Weekly instillation of mitomycin gel into the UUT for 6 consecutive weeks resulted in low systemic exposure to mitomycin and was not associated with any test-article-related adverse effects.
- Tested doses were not associated with mortality, clinical findings (observations), changes in body weight or electrocardiogram (ECG), or meaningful changes in hematology, clinical chemistry, coagulation, urinalysis, or urine chemistry parameters.
- No-observed-adverse-effect level (NOAEL) was declared to be 8 mg mitomycin/mL or a total mitomycin dose of 56 mg, which was the maximal feasible dose

Conducting Laboratory and Location:

(b) (4)

Good Laboratory Practice (GLP) compliance: Yes

Methods

Dose and frequency of dosing: Approximate dose of 14, 28, or 56 mg mitomycin (2, 4, or 8 mg/mL), instilled once weekly for 6 weeks (total of 6 instillations) with 4 weeks recovery

Route of administration: Retrograde instillations to the renal pyelocalyceal system (unilateral, left kidney)

Formulation/vehicle: Admixture/hydrogel

Species/strain: Domestic Yorkshire crossbred swine (farm pig)

Number/sex/group: Treatment: 6/female/main; 3/female/recovery
Procedure control: 4/female/main; 2/female/recovery
Vehicle control: 6/female/main; 3/female/recovery

Age: Approximately 16 to 17.5 weeks

Satellite groups/unique design: Only female pigs could be studied associated with the complicated access to the urinary tract due to the unusual penile anatomy of male pigs.

Deviation from study protocol affecting interpretation of results: No

Observations and Results: Changes From Control

Parameters	Major Findings
Mortality	All except 3 animals survived to the scheduled necropsy (1 determined to be unsuitable for study due to a perforation of the ureter was euthanized; 2 deaths were considered to be a result of the anesthesia procedures and not related to the test article or vehicle)
Clinical Signs	Clinical findings were limited to observations considered to be within normal limits for animals of this age and strain. The most common findings were changes in external appearance such as lacrimation, abrasions, and scabbed areas. In addition, several animals were considered to be warm to the touch following dosing and recovery from anesthesia. This was considered to be related to the anesthesia and not test article-related as this occurred in animals in all dose groups including controls. The elevated body temperature was managed initially with additional injections of acepromazine and external cooling.
Body Weights	Administration of the test article was not associated with any effects on body weight values over the course of the study. Animals gained weight at approximately the same

NDA 211728 Multi-disciplinary Review and Evaluation
UGN-101 (mitomycin gel) for instillation

	rate over the 6-week dosing and 4-week recovery periods. A slight decrease in body weight in the vehicle animals was noted from Week 9 to Week 10. This decrease is attributed to the fact that the mean weight only includes 2 animals, as the third animal was submitted to the scheduled necropsy the day prior to the Week 10 body weight measurement.
ECG	Qualitative and quantitative review of the ECGs obtained predose and 1 to 2 hours postdose during the first and the last week of dosing was conducted by a board-certified veterinary cardiologist. There was no test article-related effect of the treatment on qualitative or quantitative ECG parameters.
Hematology	Instillation of mitomycin gel or vehicle was not associated with any effects on hematology endpoints at any collection interval, up to and including the recovery collection.
Clinical Chemistry	Sporadic mild increases in total bilirubin concentration and sorbitol dehydrogenase activity were noted among individuals from all groups relative to individual pretest values. The changes were noted as early as the Week 1 collection, but lacked a dose response, and typically resolved among individual animals despite continued dosing. Due to the sporadic and transient nature of these changes, and similarity to changes noted in procedure and vehicle control animals, they were not considered test article-related. Sporadic mild to moderate increases in aspartate aminotransferase, creatine kinase and/or lactate dehydrogenase activity were also present among individual animals from all groups at most collection intervals, relative to individual pretest values. These changes tended to be transient, lacked a dose response, and were considered secondary to procedure-related myofiber injury. No consistent patterns of change were noted to suggest a test article-related effect. All other fluctuations among individuals and mean values, including mean values that were statistically different from the control groups, were considered sporadic, consistent with biologic variation, and/or negligible in magnitude, and not related to test article administration.
Urinalysis	Instillation of mitomycin gel or vehicle was not associated with any effects on urinalysis endpoints at any collection interval, up to and including the recovery collection. There were minor variations between treatment groups among biochemical (protein, occult blood, bilirubin, etc.) urinary components; however, all findings were considered within an acceptable range for biologic and/or procedure-related variability.
Gross Pathology	Test article-related macroscopic findings of mild to moderate swelling/thickening and/or irregular surface were seen in the left ureter of terminal females in a dose-dependent pattern in 4 mg/mL (1 of 6), and 8 mg/mL (3 of 6) mitomycin gel dose levels. Similar findings were seen in the untreated side (right ureter) of 1 of 6 terminal animals treated with 8 mg/mL and in the left ureter of a single recovery animal dosed with 8 mg/mL mitomycin gel. Procedure-related macroscopic findings of mild to moderate red discoloration or red focus/foci were seen in a non-dose-dependent pattern in the left ureter of each terminal mitomycin gel and vehicle group (2/6 at 2 mg/mL, 3/6 at 4 mg/mL, 1/6 at 8 mg/mL, and 1/6 in the vehicle group). Similar findings were seen at a low incidence in

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	the right ureter (1/6 at 8 mg/mL) and/or urethra (1/6 at 2 mg/mL and 1/6 in the vehicle group), although the findings in the right ureter could not be related to any surgical procedure. All other macroscopic observations were typical of those seen at the facility in domestic swine of the same sex and age, had similar incidence to that seen in controls, were of low/isolated frequency, were not dose-dependent, or were otherwise considered incidental.
Organ Weights	The left and right ureters of terminal females dosed with mitomycin gel at 2 mg/mL and the left ureters of terminal and recovery females dosed at 8 mg/mL had notably increased weights compared to vehicle dosed controls. Additionally, the mean weights of the left ureters of terminal and recovery females dosed with 8 mg/mL mitomycin gel were significantly increased over the mean weights of the right ureters of those females (64% and 62%, respectively). All other variations in organ weight findings between the groups were within the range of normal biological variation typically seen at the facility in domestic swine of these sexes and ages and were considered incidental, being non-dose-dependent, variable between groups, or otherwise too limited to consider as test article related.
Histopathology	Mitomycin gel-related dose-dependent microscopic findings were consistently seen in the left kidney and left ureter of terminal animals at all dose levels. Infrequent mitomycin gel-dosed terminal animals also had microscopic findings noted in the right ureter, right kidney, bladder, and urethra, although these did not have a consistent dose response. Microscopic findings trended towards resolution over the recovery period, with decreased severity and incidence after the recovery phase, but most did not fully resolve in all animals, with the exception of the finding of erosion. 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. The microscopic findings noted in the kidney were confined to the pelvis, involving the urothelium (urothelial vacuolation, hypertrophy, and erosion) and submucosa (edema, mixed leukocyte infiltrates, and hemorrhage). These form an interconnected constellation of associated mitomycin gel-related microscopic findings that occurred in a generally dose-dependent pattern of increasing severity and/or incidence with escalating dose in terminal animals. Severity and incidence were generally reduced in recovery animals, without a clear dose response to these combined findings. Similar microscopic findings were noted in the ureter, particularly the left ureter, and represent a similar constellation of mitomycin gel-associated changes. The majority of the ureter findings were seen in the proximal portion of the ureter, with the mid-section being generally least affected. Infrequently, findings of urothelial vacuolation and mixed leukocyte infiltration were seen in the urinary bladder and urethra of mitomycin gel-treated animals at an incidence and/or severity above that of controls. These findings were more pronounced and dose dependent in terminal females, with reduced incidence and/or severity in recovery females, where there was no clear dose response. Findings of urothelial vacuolation, urothelial hypertrophy, erosion, and inflammatory

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	infiltrates were similar in nature to the findings described in the literature for intravesicular mitomycin treatment. All other microscopic findings in these animals were typical of those seen at the facility in domestic swine of this sex and age, had a similar incidence to that seen in controls, were of low/isolated frequency, were not dose dependent, or were otherwise considered incidental.
Other Evaluations	Urine chemistry: Instillation of mitomycin gel or vehicle was not associated with any effects on urine chemistry endpoints at any collection interval, up to and including the recovery collection. Significant variation in electrolyte excretions (as measured by fractional excretion and mg/16 hour), creatinine clearance, and urea nitrogen/creatinine ratios were noted among individuals from all treatment groups. Individual values generally overlapped with those in the procedure control group, and no consistent patterns of change were noted to suggest a treatment-related effect. Coagulation times: Instillation of mitomycin gel or vehicle was not associated with any effects on coagulation times (ie, APTT or prothrombin time) or fibrinogen concentration at any collection interval, up to and including the recovery collection.
APTT = Activated Partial Thromboplastin Time; ECG = electrocardiogram.	

The Applicant's Position:

In this study of repeated instillations into the renal pyelocalyceal system, the animal NOAEL of 8 mg/mL (56 mg) was the highest dose tested. Therefore, it is likely that the margin of safety is even larger than calculated. Since the animal NOAEL dose was a maximal feasible dose using a maximal feasible formulation concentration and instillation volume for this species, this margin of exposure is considered supportive of the safety of the human dose for a chemotherapeutic agent.

Taken together, toxicology data submitted for this NDA and the toxicology profile of the approved reference listed drug, mitomycin support both the systemic and local safety of the UGN-101 clinical dose of 60 mg of mitomycin in 15 mL of mitomycin gel (4 mg/mL mitomycin).

The FDA's Assessment:

In general, FDA agrees with the Applicant's assessment. See table below for severity and incidence of microscopic findings.

Table 3: Drug-Related Microscopic Findings in Pigs After Repeated Instillations of Mitomycin Gel Administered to the Upper Urinary Tract

Dose (mg/mL)	0		2		4		8		TC-3	
Day	37	64	37	64	37	64	37	64	37	64
n	4	2	6	3	6	3	6	3	6	3
Kidney, Left										
<i>Edema, pelvis</i>										
Minimal			5	3	4	3	2	2	2	2
Mild					1		4			
<i>Erosion</i>										
Minimal			1		1					

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Version date: July 24, 2019 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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<i>Hemorrhage, pelvis</i>	Mild						2			
<i>Hypertrophy, urothelial</i>	Minimal		1		2	1	2	1	1	
	Minimal				4		3	1	1	
<i>Vacuolation urothelial</i>	Mild				1		2			
	Minimal		3	1	2	1	2	3	5	
	Mild		1	1	4	1	4			
<i>Infiltration, mixed leukocyte, pelvis</i>	Minimal		1	2	1	1	3	3	3	2
	Mild			3	1	4	3			
Kidney, Right										
<i>Edema, pelvis</i>										
	Minimal		1		3	1	1	1		1
<i>Hypertrophy, urothelial</i>	Minimal				1					
<i>Vacuolation urothelial</i>										
	Minimal		1	2	2	1	3	2	4	2
	Mild				1					
<i>Infiltration, mixed leukocyte, pelvis</i>	Minimal		1	1	1	1	1		2	2
Ureter, Left (Combined*)										
<i>Edema, pelvis</i>										
	Minimal		1	6	3	10	5	12	5	6
	Mild					2		5		1
<i>Erosion</i>										
	Minimal		1					2		
	Mild							1		
<i>Hemorrhage</i>										
	Minimal		1		3			4		1
	Mild		1							
<i>Hypertrophy, urothelial</i>										
	Minimal		2		8	3	12			
	Mild				1		1			
<i>Vacuolation urothelial</i>										
	Minimal		7	5	10	5	10	1		
	Mild		3		3		5			
	Moderate				1					
<i>Infiltration, mixed leukocyte</i>										
	Minimal				1		1		2	
	Mild				2		3			
<i>Infiltration, mononuclear cell</i>										
	Minimal	4	2	8	3	9	3	14	4	5
	Mild			1		3				1
Ureter, Right (Combined*)										
<i>Edema, pelvis</i>										
	Minimal		1	1	4	2	4	5	2	2
	Mild					1				
<i>Hemorrhage</i>										
	Minimal		1							
<i>Hypertrophy, urothelial</i>										
	Mild							1		
<i>Vacuolation urothelial</i>										
	Minimal				1	1				
	Moderate							1		
<i>Infiltration, mixed leukocyte</i>										
	Mild				1		1			
<i>Infiltration, mononuclear cell</i>										
	Minimal	1		1	3	3	2	5	3	4

One recovery sow in Group 5 was terminal sacrificed on Day 63, instead of Day 64.

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*: Evaluation results from several samples from a ureter were evaluated and results reported in combination.

General Toxicology; Additional Studies

The Applicant's Position:

As a 505(b)(2) NDA, no additional GLP studies were conducted to evaluate general toxicology. The toxicology of mitomycin is well described in the scientific literature and in association with the approved drug product (RLD), Mutamycin, and as referenced ([Accord Healthcare 2014](#)). In addition to the available literature, several investigative (non-GLP) nonclinical studies were conducted prior to the main GLP study (Study 2189-007) to determine appropriate dosing procedures, doses, dose volumes, and general study conditions and parameters, as detailed in NDA Section 2.6.6.

The FDA's Assessment:

FDA agrees with the Applicant's statement. The GLP repeat-dose toxicology study in pigs adequately evaluated the nonclinical safety of mitomycin gel in the upper urinary tract, and additional general toxicology studies were not needed to support a marketing application for Jelmyto.

5.5.2. Genetic Toxicology

The Applicant's Position:

As a 505(b)(2) NDA, no genotoxicity studies were conducted for this application. The toxicology of mitomycin is described in the scientific literature ([Macgregor et al. 1990](#) and [Mori et al. 1984](#)) and in association with the approved drug product (RLD), Mutamycin, and as referenced ([Accord Healthcare 2014](#)).

The FDA's Assessment:

FDA agrees with the Applicant relying on FDA's previous findings of safety for Mutamycin. The referenced publications were not reviewed or needed to support a marketing application for Jelmyto.

5.5.3. Carcinogenicity

The Applicant's Position:

Mitomycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical dose in humans, mitomycin produces a greater than 100% increase in

tumor incidence in male Sprague-Dawley rats and a greater than 50% increase in tumor incidence in female Swiss mice (Accord Healthcare 2014).

The FDA's Assessment:

FDA agrees with the Applicant relying on FDA's previous findings of safety for carcinogenicity. Of note, the recommended clinical dose in humans specified above by the Applicant was for an intravenous dose of mitomycin in humans rather than for retrograde instillation for Jelmyto.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Safe use of mitomycin in pregnant women has not been established. Teratological changes have been noted in animal studies (Bishop et al. 1997 and Gregg and Snow 1983). The effect of mitomycin on fertility is unknown (Accord Healthcare 2014).

The FDA's Assessment:

FDA agrees with the Applicant relying on FDA's previous findings of safety for reproductive and developmental toxicity. The referenced publications were not considered relevant as the route of administration was intraperitoneal injection and not instillation into the pyelocalyceal system. Dedicated fertility studies were not needed to support a marketing application for Jelmyto for the proposed indication.

5.5.5. Other Toxicology Studies

Applicant's Position:

Local Tolerance; UroGen Study NLI 569493: The study evaluated the irritation potential of the sterile hydrogel. Hydrogel was diluted to a concentration of 35% in order to enable instillation into the rabbit bladder through a catheter and to assess bladder irritation after application for 5 consecutive days. No signs of discharge, erythema, or edema were observed at any of the observation points. Macroscopic observations of the bladder, urethra, and vagina at necropsy revealed no significant findings. Histological evaluation resulted in an irritation index of 0.0. Thus, the test article extract was considered a non-irritant to the bladder tissue of New Zealand white rabbits.

Cytotoxicity; UroGen Study NLI 561378: The cytotoxicity of diffusible components of hydrogel was assessed using the Agar Overlay assay. A layer of agar was added over a cell monolayer to act as a cushion to protect the cells from mechanical damage while allowing the diffusion of

leachable materials. The test articles were then placed on top of the agar layer and incubated. The cell monolayers were examined and scored based on the degree of cellular destruction. All test method acceptance criteria were met. No cytotoxic effects of the hydrogel were noted.

Sensitization; UroGen Study NLI 567039: Evaluation of the allergenic potential or sensitizing capacity of the hydrogel was assessed in guinea pigs. In the preliminary irritation phase, the topical application of all concentrations of the hydrogel elicited no reaction at 24 hours. Intradermal injection of the test article caused severe erythema and mild edema at the 100%, 75%, and 50% concentrations. Therefore, the test article was used at the 100% concentration for the induction application and at the 100% concentration for the topical and challenge applications. None of the hydrogel-treated or negative control animals (NaCl) exhibited any reaction to the challenge (0% sensitized). As defined by the Kligman scoring system, the reaction was defined as a Grade I reaction and the test article is classified as having weak allergenic potential. Based on the protocol criteria, the Grade I sensitization rate is not considered significant.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Impurities/Degradants

The CMC review team requested nonclinical input on the specified drug product impurities in the table below. Specified impurities 4 and 5 were within the qualification threshold recommended by ICH Q3B, taking into consideration intermittent dosing and recommendations on impurities outlined in ICH S9 and ICH S9 Q&A for patients with advanced cancer. Specified impurities 1 and 3 were present at higher levels in the toxicology batches and were qualified. For specified impurity 2, patients receiving the recommended intravesical dose of 60 mg mitomycin gel (4 mg/mL) will receive (b) (4) impurity 2. In GLP toxicology studies, animals received up to (b) (4) impurity 2 following weekly intravesical administration of mitomycin gel. In addition, the Applicant conducted a side-by-side comparison with the listed drug following preparation instructions in the FDA-approved label (storage conditions up to 7 days at room temperature). At ≥24 h, mitomycin samples had comparable levels of impurity 2. Thus, there are no safety concerns with the levels of specified impurities in the drug product for the proposed patient population.

Impurity Name	RRT	RRF	Proposed Spec.	Qualified in Tox at 4 mg/mL (HP1)	Qualified in Tox at 4 mg/mL (HP2)
1)	(b) (4)				
2)					

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3)	(b) (4)
4)	
5)	

HP: Holding Period

Extractables and Leachables

The Applicant conducted extractable and leachable experiments for the processing materials and the container closure system used for (b) (4) sterile hydrogel (the carrier matrix) and mitomycin for solution separately. (b) (4)

ICH S9 and ICH S9 Q&A, applying a more conservative approach is unnecessary for the proposed patient population. In addition, the total daily intake of leachables are below the qualification limits recommended in ICH Q3 guidances. While these guidances are not entirely applicable to leachables, the principles can be applied given the patient population, genotoxic product, low systemic exposure, and local and intermittent administration. Thus, there are no safety concerns with leachables from the processing materials or container closure system.

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George Ching-Jey Chang
Primary Reviewer

Tiffany Ricks
Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The proposed dose of UGN-101 of 4 mg/mL, is individualized based on the volumetric measurement of a patient's pyelocaliceal system, up to a maximum dose of 60 mg of mitomycin or 15 mL, whichever is lower. The efficacy and safety of UGN-101, at the proposed dose of 4 mg/mL to a maximum dose of 60 mg, in patients with low-grade upper-tract urothelial cancer was supported by the results of the pivotal Phase 3 study UT001.

The key review issue focuses on the systemic exposure of UGN-101.

Following instillation into the pyelocaliceal system, UGN-101 forms a semisolid gel which dissolves from normal kidney urine flow releasing mitomycin for up to 4 to 6 hours. Mitomycin is eliminated unchanged in the urine. The concentrations of mitomycin in plasma were variable and ranged from 2.43 to 12.80 ng/mL over the course of treatment. The mean C_{max} was 6.24 ng/mL, which is estimated to be less than 1% of that after intravenous administration. Systemically absorbed mitomycin is rapidly cleared from the serum, approximately 10% is excreted unchanged in the urine. Since the systemic exposure following administration of UGN-101 is minimal compared to IV administration, there are no systemic safety concerns with UGN-101.

Recommendation: The Office of Clinical Pharmacology has reviewed the information contained in NDA 211728. This NDA is approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

This application relied on the FDA's previous review of the RLD and publicly available scientific literature to describe the clinical pharmacology of mitomycin. UroGen also conducted planned pharmacokinetic (PK) evaluations in a subset of patients (N = 6) enrolled in Study UT001. Blood samples were collected at 0 minutes (pre-dose) and 30 minutes, 1, 2, 3, 4, 5, and 6 hours following the first instillation.

The plasma concentration versus time average profile showed that at 6 hours post-instillation, the average plasma concentration was less than 2 ng/mL. The mean C_{max} was 6.24 ng/mL (range: 2.43 to 12.80 ng/mL), and the time to C_{max} (T_{max}) was 1.79 hours (range: 0.50 to 5.17 hours) after instillation. The highest individual observed C_{max} value of 12.80 ng/mL was 187-fold and 40-fold lower than the observed C_{max} level following an intravenous bolus dose of 30 mg or 10 mg mitomycin (2.4 µg/mL and 0.52 µg/mL, respectively) and is 31-fold lower than

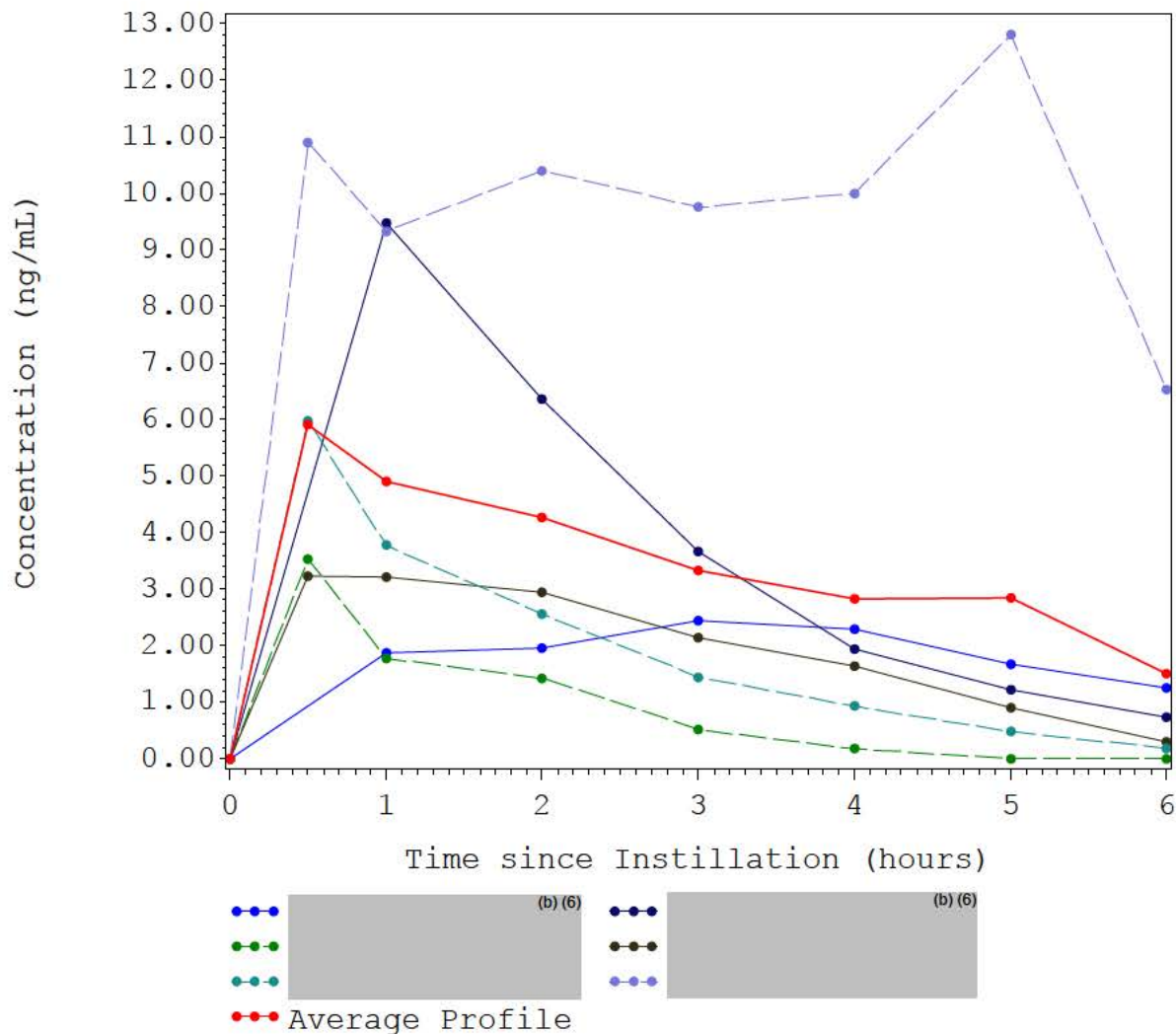
the threshold value of 400 ng/mL for myelosuppression observed with mitomycin (Crooke et al. 1976).

The mean total systemic exposure to mitomycin up to 6 hours post-instillation area under the concentration-time curve from 0 to 6 hours ($AUC_{(0-6)}$) was 20.30 ng·hr/mL (range: 5.64 to 58.76 ng/hr/mL). Patient (b) (6) did not exhibit a terminal log-linear phase in the concentration-time data; therefore, no values for AUC from 0 to infinity (AUC_{inf}), elimination rate constant (λ_z), or terminal half-life ($t_{1/2}$) were reported for this patient.

The mean $t_{1/2}$ following instillation of mitomycin into the UUT was 1.27 hours (76 minutes), which was longer than the true $t_{1/2}$ of mitomycin following a 30-mg bolus injection (mean $t_{1/2}$ value of approximately 17 minutes). The apparent $t_{1/2}$ demonstrates that UGN-101 dissolved gradually, resulting in prolonged exposure of mitomycin following local instillation into the UUT.

The concentration-time curve is presented in Figure 1. Summaries of PK parameter values are presented in Table 3 and Table 4.

Figure 1 Concentration-Time Curve (PK Analysis Set)



PK = pharmacokinetic.

Source: Study UT001 CSR Figure 14.4.3.

Table 4 Mitomycin Concentration in K₂EDTA Human Plasma (ng/mL) by Time (Study UT001 - PK Analysis Set)

Sample Collection Time	n	Mean (SD)	Median (Range)
Pre-instillation	6	0.00 (0.00)	0.00 (0.00, 0.00)
0.5 hours post-instillation	4	5.91 (3.55)	4.75 (3.22, 10.90)
1 hour post-instillation	6	4.90 (3.57)	3.49 (1.77, 9.47)
2 hours post-instillation	6	4.27 (3.47)	2.75 (1.42, 10.40)
3 hours post-instillation	6	3.32 (3.32)	2.29 (0.51, 9.75)
4 hours post-instillation	6	2.83 (3.60)	1.79 (0.17, 10.00)
5 hours post-instillation	6	2.84 (4.91)	1.06 (0.00, 12.80)
6 hours post-instillation	6	1.49 (2.50)	0.51 (0.00, 6.52)

K₂EDTA = dipotassium ethylenediaminetetraacetic acid, PK = pharmacokinetic.

Concentrations below the limit of quantification were replaced by 0.

Source: Study UT001 CSR Table 14.4.1.

Table 5 Summary of Pharmacokinetic Parameters (PK Analysis Set)

Screening Number	C _{max} (ng/mL)	T _{max} (h)	AUC ₍₀₋₆₎ (ng•hr/mL)	λ _z (h ⁻¹)	t _½ (h)	AUC _{inf} (ng•hr/mL)
(b) (6)	2.43	2.92	10.72	0.30	2.28	14.79
	9.47	0.98	23.10	0.49	1.42	24.60
	3.53	0.50	5.64	1.03	0.67	5.80
	3.22	0.58	11.82	0.83	0.84	12.17
	5.97	0.58	11.78	0.60	1.16	12.09
	12.80	5.17	58.76			
Mean (SD)	6.24 (4.11)	1.79 (1.89)	20.30 (19.69)	0.65 (0.28)	1.27 (0.63)	13.89 (6.84)
Geometric Mean (CV)	5.21 (0.73)	1.17 (1.26)	15.01 (0.95)	0.60 (0.50)	1.16 (0.50)	12.54 (0.56)

λ_z = elimination rate constant; AUC₍₀₋₆₎ = area under the plasma concentration-time curve from 0 to 6 hours;

AUC_{inf} = area under the plasma concentration-time curve from 0 to extrapolated infinity; C_{max} = highest concentration achieved in plasma; CV = coefficient of variation; PK = pharmacokinetic; t_½ = terminal half-life;

T_{max} = time to highest plasma concentration.

Source: Study UT001 CSR Table 14.4.2.

The Applicant's Position:

The local administration of mitomycin in a gel formation is associated with markedly lower systemic exposure to mitomycin compared to systemic administration. As demonstrated by the scientific literature and nonclinical studies, enhanced mitomycin activity may be achieved by increasing mitomycin dwell times, which in turn may increase the drug concentrations in the target tissues (Section 5.4), without a significant increase in plasma mitomycin concentration, hence resulting in less systemic toxicity (Section 5.5.1).

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

6.2.2. General Dosing and Therapeutic Individualization

6.2.3. General Dosing

The Applicant's Position:

The volume of UGN-101 administered in the pivotal Phase 3 study (Study UT001) was individualized based on volumetric measurements of each patient's pyelocalyceal system using pyelography, up to a maximum dose of 60 mg mitomycin (the volume of UGN-101 instilled was 100% of the estimated pyelocalyceal volume or 15 mL, whichever was lower). Enrolled patients received 6 once-weekly unilateral retrograde instillations. Patients with a response of CR at the primary disease evaluation (PDE) visit (PDE_{CR}) were to undergo up to 11 additional once-monthly maintenance instillations of UGN-101.

Due to the limited systemic exposure to mitomycin following local application, no blood level-response relationship of effectiveness contributed to dose selection or choice of dose interval. Dose selection and choice of dose interval was based on the experience with mitomycin in the bladder, supported by nonclinical studies, and data from the Compassionate Use Program, thus no additional examination of dose response was completed.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

6.2.4. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors (body weight, age, gender) or in special populations (hepatic or renal impairment) including patients with only 1 kidney. Dose is individualized based on the volumetric measurement of the patient's pyelocalyceal system.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

6.2.5. Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:

FDA agrees.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

The application refers to the NDA for the Listed Drug, and FDA's previous findings on the safety and efficacy of mitomycin.

Non-clinical and clinical pharmacology: Pharmacology parameters were restricted to discussion of the pharmaceutical active agent mitomycin in this NDA. The overall pharmacology for mitomycin is well described in the scientific literature. The mechanism of tumor cell destruction by mitomycin is largely ascribed to DNA alkylation and consequent inhibition of DNA synthesis. Modification of redox cycling, ribosomal RNA inhibition, and modulation of thioredoxin reductase activity are additional activities of mitomycin. In UGN-101, mitomycin is expected to act as a cytotoxic agent following release from the hydrogel.

Pharmacokinetics: The prolonged retention of UGN-101 is considered likely to be associated with maintenance of increased local levels of mitomycin, whereas normal urine flow and the absence of reservoir capability significantly limit the contact time of aqueous drug solutions applied to the UUT.

The gradual dissolution of UGN-101 results in prolonged exposure of mitomycin following local instillation into the UUT (mean apparent plasma $t_{1/2}$: 1.27 hours [76 minutes]). However, prolonged dwell times for mitomycin do not appear to result in increased systemic toxicity, and instillation of UGN-101 to the renal pyelocalyceal system results in reduced systemic absorption of mitomycin (mean C_{max} = 6.24 ng/mL [Range: 2.43 to 12.80 ng/mL]; $AUC_{(0-6)}$ = 20.30 ng•hr/mL).

The FDA's Assessment:

FDA agrees with the applicant's assessment.

6.3.2. Clinical Pharmacology Questions

- 6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

The clinical pharmacology of UGN-101 is based on the pharmaceutical active agent mitomycin and described in the scientific literature in association with the approved RLD.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

- 6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

The proposed dosing regimen was studied in clinical Study UT001 and is appropriate for the general patient population of LG UTUC. The details of the proposed dose are presented in Section 6.2.3.

The FDA's Assessment:

FDA agrees with the applicant's position.

- 6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in special populations (ie, hepatic and renal impairment).

The FDA's Assessment:

FDA agrees with the applicant's assessment.

- 6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

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No clinically relevant food-drug or drug-drug interactions are reported for the RLD, mitomycin. There are no additional drug-drug interactions to be considered based on the route of administration of UGN-101.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

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Catharine Bulik
Primary Reviewer

Pengfei Song
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position

Table 6 Listing of Relevant Clinical Trials

Trial ID	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
<i>Pivotal Study to Support Efficacy and Safety (Indication: LG UTUC)</i>								
UT001	02793128	Prospective, open-label, single-arm, pivotal Phase 3 study	UGN-101; 4 mg/mL (volume administered dependent upon pyelocalyceal volume); unilateral retrograde instillation TP: 6 once-weekly instillations MP: 11 once-monthly instillations	Primary: proportion of patients attaining CR at the end of the PDE Visit Key secondary: durability of CR at 12 months post-PDE Secondary: durability of CR at 3, 6, and 9 months post-PDE and clinical benefit for patients with partial response at the PDE Visit	Treatment: 6 weeks of treatment plus 5 weeks (± 1 week) to the PDE Visit Follow-up: from up to 3 weeks post PDE Visit, to up to 12 months (± 2 weeks) post PDE Visit	74	Patients with naïve or recurrent LG, noninvasive UTUC in the pyelocalyceal system and documented absence of HG UC, diagnosed not more than 2 months prior to the screening.	24 (enrolled patients); US, Israel
<i>Other Studies to Support Efficacy and Safety (Indication: MIBC/NMIBC)</i>								
BL001	01648010	Single-dose, non-randomized, open-label	Hydrogel and UGN-102 (1 mg/mL); intravesical instillation	Short-term safety and tolerability	Single dose, with FU until RC	8	Patients with bladder cancer who were about to undergo radical cystectomy	1; Israel
BL002	01803295	Non-randomized, open-label, dose-escalation	40 mg UGN-102 or 80 mg UGN-102; 6 once-weekly intravesical instillations	Primary: subjects degree of response 2 to 4 weeks post treatment Secondary: tumor recurrence rate during the 12 months post-2 to	6 weeks with FU until 12 months post TURBT	18	Patients with NMIBC, pre-TURBT	1; India

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Trial ID	NCT No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
				4-week FU in CR patients and lesion mass by time point				
BL003	01799499	Randomized, open-label, active-control	40 mg UGN-102 80 mg UGN-102 40 mg mitomycin in water; 6 once-weekly intravesical instillations	Frequency of CR Status at FU 2-4 Week Post Instillations Lesion size and response status	6 weeks with 12 month follow-up	81	Patients with NMIBC, pre-TURBT	13; Israel, Italy, Spain, and Switzerland
BL004	02307487	Open-label, dose-escalation	120 mg UGN-102 140 mg UGN-102 160 mg UGN-102	CR rate defined as percent of patients with CR at the PDE Visit. Durability: CR rate defined as percent of patients who continued to display CR at 3, 6, 9 and 12 months following the last treatment.	6 weeks with 12 month follow-up	14	Patients with NMIBC, pre-TURBT	2; Israel

Note: Study UT001 was previously known as Study TC-UT-03. Study BL001 was previously known as Study TC-RC-01/2-R and Study TAS-4M-PR-H-127-1. Study BL002 was previously known as Study TC-BC-02-R. Study BL003 was previously known as Study TAS-4M-CS-0002-R. Study BL004 was previously known as Study TC-BC-10. Study BL004 was terminated early before escalation to the 140 mg or 160 mg UGN-102 cohorts. The same doses of UGN-102 (40 mg and 80 mg) were used in BL002 and BL003, but were described in the BL003 clinical study report (CSR) as 37.5 mg and 75 mg, respectively.

CR = complete response; FU = follow up; HG = high grade; LG UTUC = low-grade upper tract urothelial carcinoma; MIBC = muscle-invasive bladder cancer; MP = maintenance period; NMIBC = non-muscle invasive bladder cancer; PDE = Primary Disease Evaluation; RC = radical cystectomy; UC = urothelial cancer; US = United States; TURBT = transurethral resection of bladder tumor; TP = treatment period.

Source: Studies UT001, BL001, BL002, BL003, BL004.

The FDA's Assessment:

FDA agrees with the Applicant's position. Analysis of results from one clinical trial, UT001 (OLYMPUS), forms the primary basis for efficacy and safety analysis. The Applicant additionally submitted uncontrolled narrative data from compassionate use program for UGN101 in LG

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UTUC to provide evidence of the long-term durability of CR. The supportive studies provided by the Applicant use UGN-102, which consists of hydrogel combined with a lower concentration of mitomycin as compared to UGN101, as the study treatment for bladder cancer. Because these are different drugs and patient populations, the results from these supportive studies were not considered in support of the Applicant's efficacy and safety claims for UGN-101 in LG-UTUC.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study UT001

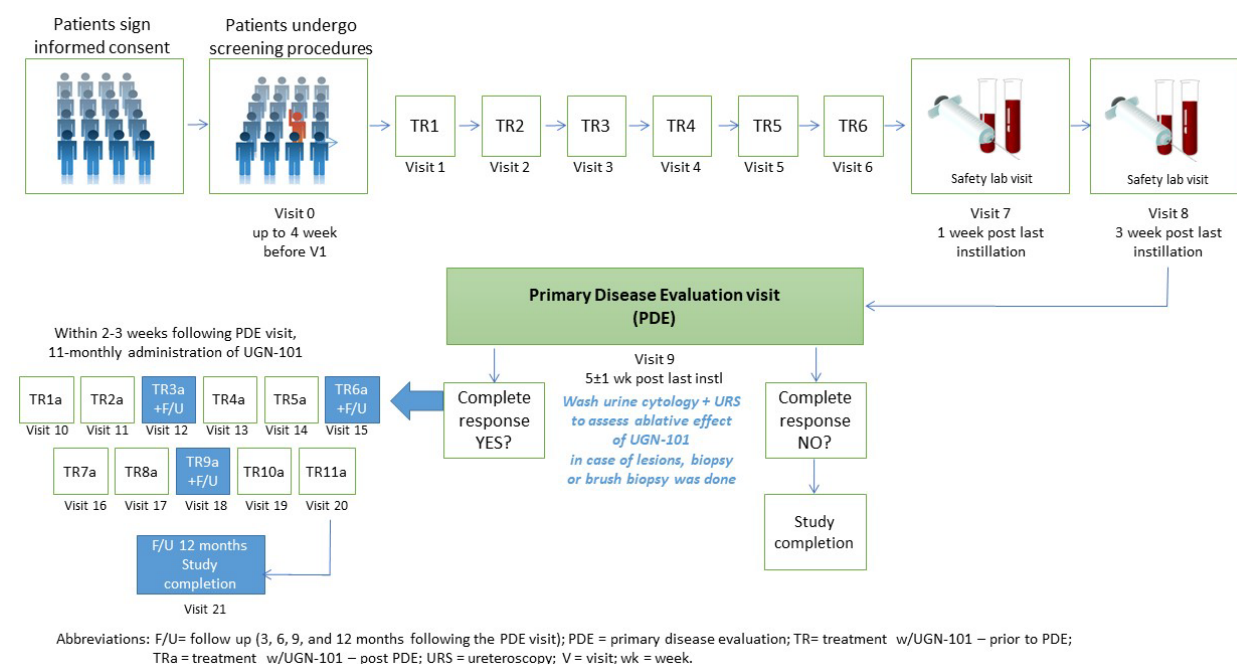
8.1.1.1. Trial Design

The Applicant's Description:

Basic Study Design

Study UT001 is a prospective, open-label, single-arm Phase 3 pivotal study, designed to assess the efficacy, tolerability, and safety of UGN-101 treatment administered to the UUT. Naïve or recurrent patients with LG, noninvasive UTUC in the pyelocalyceal system, as initially determined by a local pathologist's evaluation of biopsy and UUT cytology slides and confirmed by the investigator and a central laboratory, were enrolled. A schematic of the study design is presented in Figure 2.

Figure 2 Study Flow Chart for Protocol TC-UT-03



Trial location

Twenty-four (24) sites in the US and Israel enrolled patients.

Choice of control group

This trial is a single arm design. There is no comparable, non-surgical “ablative” therapy to which UGN-101 can be compared. In addition, UGN-101 is proposed as a nephron sparing approach for patients who would otherwise be candidates for RNU, therefore, neither equivalent control nor placebo arms were considered due to ethical reasons.

Diagnostic criteria

Patients with identified LG, noninvasive UTUC in the pyelocalyceal system, as determined by a local pathologist’s evaluation of biopsy and UUT cytology slides and confirmed by the Principal Coordinating Investigator, were enrolled. Refer to study design section above.

Key inclusion/exclusion criteria

The patient population in Study UT001 consisted of naïve or recurrent adult patients with LG, noninvasive UTUC in the pyelocalyceal system and documented absence of HG urothelial carcinoma (UC), diagnosed not more than 2 months prior to the screening. Patients were to have at least 1 measurable papillary LG tumor at least 5 mm and the largest lesion was not to exceed 15 mm. Patients were not eligible for the study if they had received Bacille Calmette Guérin (BCG) treatment for UC within 6 months of Visit 1, had untreated concurrent UC in other locations other than the target area (unless treated during screening), had a past history of carcinoma in situ in the urinary tract, had a history of invasive UC within the previous 5 years, or had a history of HG papillary UC in the urinary tract (during the past 2 years). Patients actively being treated with systemic chemotherapy or with the intent to be treated during the duration of the study were also excluded from the study.

Dose selection

The dose selected (4 mg/mL) allowed a safety margin; while the dosage (6-weekly instillations) was consistent with the dosage of mitomycin used for intravesical instillations and in post/peri-operative instillations in the UUT (Mohamed et al. 2011).

Due to the inter-individual variability in the anatomy and volume of renal pelvis and calyces, the volume of the UGN-101 for instillation was determined for each patient individually by the investigator, based on volumetric estimation using retrograde pyelography for injecting the contrast agent (maximal volume required to fill the pyelocalyceal space).

Study treatments

UGN-101 (4 mg mitomycin per mL of sterile hydrogel; administered volume dependent upon pyelocalyceal volume) was administered by retrograde instillation via ureteral catheter.

Assignment to treatment

All patients in the study received UGN-101 at 4 mg/mL

Blinding

This was an open-label, single-arm trial.

Dose modification, dose discontinuation

Discontinuation from UGN-101 treatment was mandated for the adverse events (AEs) of Grade 4 Neutropenia lasting more than 5 days, Febrile neutropenia, Grade 4 Thrombocytopenia, Grade 3 Thrombocytopenia with hemorrhage, Grade 3 to 4 non-infective cystitis, Grade 3 to 4 Hematuria, urinary system perforation (any grade), and Grade 4 non-hematologic toxicity (except Grade 4 Vomiting/Diarrhea lasting less than 72 hours in the absence of maximal medical therapy and Grade 4 laboratory abnormalities that could be readily corrected and did not result in hospitalization). Discontinuation from UGN-101 treatment was also mandated for a dose delay of more than 4 weeks due to an adverse reaction.

No dose modifications or delays were to be allowed in patients who did not tolerate UGN-101. These patients were discontinued from the study treatment.

Administrative structure

Trial oversight was managed by:

- o An external, independent data monitoring committee (DMC), comprised of urologists, a nephrologist, and a statistician was assigned to this study. Safety and efficacy data were monitored by the DMC according to schedule and scope defined in the DMC charter.
- o A Study Steering Committee, which consisted of the Principal Coordinating Investigator and members of the TC-UT-03 study team, governed the conduct of the study and made the final decision on any protocol modifications. The steering committee also reviewed the DMC recommendations and could initiate ad hoc DMC meetings, as needed.

At each center, the Principal Investigator was responsible for the study conduct. Dr. Seth Lerner, MD was appointed as Principal Coordinating Investigator for the study.

Procedures and schedule

A general description of study visits is presented in Table 6.

Table 7 General Description of Study Visits

Period	Visit	Timeline
Screening	Visit 0	Up to 4 weeks prior to treatment
Treatment	Instillations 1 to 6 (Visit 1 to 6)	Once weekly for 6 weeks
	Safety Labs (Visit 7 to 8)	One week and 3 weeks post last instillation
	PDE (Visit 9)	5 ± 1 weeks following the last instillation visit
Maintenance and Follow up	Maintenance Instillations (Visit 10 to 20)	Within 2 to 3 weeks following PDE Visit, 11 monthly administrations of UGN-101
	Follow-up visits (Visits 12, 15, 18, and 21)	3, 6, 9, and 12 months post-PDE Visit

PDE = Primary Disease Evaluation

Concurrent medications

The use of several non-study drugs was defined in the protocol, as described below:

- **Sodium Bicarbonate:** The patient was given 1.3 g sodium bicarbonate tablets and written instructions/dosing diary. The sodium bicarbonate was to be consumed orally the night before the instillation, the morning of instillation, and 30 minutes prior to the instillation procedure (total of 3.9 g). If the patient was planned to be anesthetized, sodium bicarbonate was not to be taken within 30 minutes prior to the treatment.
- **Diuretics:** It was preferred that diuretics were not taken the night before and prior to the instillation. If a patient was on diuretic medications, the Principal Investigator determined if the medication could be skipped prior to the instillations as recommended. Patients were also advised on the use of diuretics during the study.
- **Prophylactic Antibiotics:** To minimize the risk for urinary tract infection (UTI), especially acute pyelonephritis, antimicrobial prophylaxis (eg, ciprofloxacin) was suggested according to the American Urological Association Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis.
- **Prophylactic Anti-allergic Treatment:** Prophylactic anti-allergic treatment was given according to Investigator discretion. The recommended regimen was to take antihistamine agents the day before instillation, on the day of instillation, and 1 to 3 days post-instillation.
- **Diazepam (or Any Other Oral Sedative):** Diazepam (5 to 10 mg tablets) or any other sedative was given according to Investigator discretion as an optional therapy to reduce anxiety before each instillation. The dose was to be given an hour before instillation. The patient was advised of compromised driving ability on that day.
- **Skin Ointment:** Prior to instillation, local ointment was used to protect the skin and reduce irritation around the genitalia. Female patients were instructed to carefully wash the genitalia following each urination during the day of instillation, and then apply the local ointment on the genitalia.
- **Treatments as Needed:** Dysuria was managed through the administration of local and systemic analgesics. Lower urinary tract symptoms such as frequency, urgency, and incontinence were managed through the use of anticholinergic agents, if not contraindicated.

Exclusions relating to prior or concomitant medications were determined when their administration potentially confounded the safety and efficacy of the study drug. The following concomitant medications were prohibited during the study: systemic chemotherapy, intravesical chemotherapy (full course), and BCG.

Treatment compliance

Study drug compliance, including the actual dose of study drug administered, was documented in the administration form and monitored at the sites. No effectiveness assessment was based on compliance.

Subject completion, discontinuation, or withdrawal

- o **Trial Completers:** Patients defined as partial or no response (PR or NR) at the PDE Visit were considered to be trial completers at that visit. Patients defined as CR at the PDE visit were considered to be trial completers when and if tumor recurred during FU, or when the patient completed the 12-month FU visit.
- o **Discontinuation or withdrawals:** Patients who discontinued treatment were not replaced and missing values for these patients were handled as specified in the statistical analysis plan (SAP) based on the Analysis Set.
 - o In the intent-to-treat (ITT) analysis set (used for the primary endpoint), patients with no observed value on primary efficacy were imputed as "Failure" for the primary efficacy endpoint if they dropped out from the study before the PDE evaluation. Patients who were considered indeterminate at the PDE Visit, either due to "undetermined" response recorded on the case report form (CRF) or to unavailable results, and who were considered as CR at subsequent visits were not imputed as "Failure".
 - o In the patients defined as CR at the PDE visit (PDE_{CR}) Analysis Set (used for the key secondary endpoint), missing data for patients who remained in the study but had no follow-up visits following their PDE evaluation were imputed for time-to-recurrence as censored from the day following the PDE Visit. For patients with at least one Follow-up Visit, the time-to-recurrence was based on the observed data (as event or censored). Censoring for time-to analysis was determined based on the last available observation for the patient. For patients who completed or discontinued, time-to-recurrence was censored at the date of completion or discontinuation, respectively. For patients for whom response was indeterminate, censoring was at the last available visit.

The FDA's Assessment:

FDA agrees with the Applicant's description of Study UT001 above. Sodium bicarbonate administration was administered to alkalize the urine, which has been reported to increase the stability and efficacy of aqueous mitomycin. FDA notes the following additional details of the study design:

1. Patients were allowed to receive tumor debulking subsequent to an initial evaluation but prior to the first treatment visit as long as there was a remaining papillary LG tumor of at least 5mm that was visualized at the Screening Visit. The Applicant reported that 26 patients underwent tumor debulking within 6 weeks of initial treatment to meet the enrollment criteria of UT001. Debulking appears appropriate because the local antitumor effect could potentially be decreased for the larger tumors.
2. The volume of UGN101 was based on estimated pyelocaliceal volume, but all patients received the same concentration of UGN101 at 4 mg/mL. In addition, the physician was allowed to remeasure the volume, and adjust based on patient comfort, or physician

discretion.

3. Patients were eligible for enrollment into the Maintenance Period of UT001 if they demonstrated a Complete Response (CR) at the PDE visit at 3 months following treatment initiation. During the Maintenance Period, patients were allowed to receive up to 11 monthly instillations of UGN. Follow-up visits were scheduled at 3, 6, 9, and 12 months after a CR, where a review of unresolved AE's and new AEs, upper tract washing urine cytology at every visit, and CTU performed at the 12-month follow-up visit.
4. Investigator-assessment of tumor response is subject to bias. The Sponsor included central review of histopathology and cytology to address this.

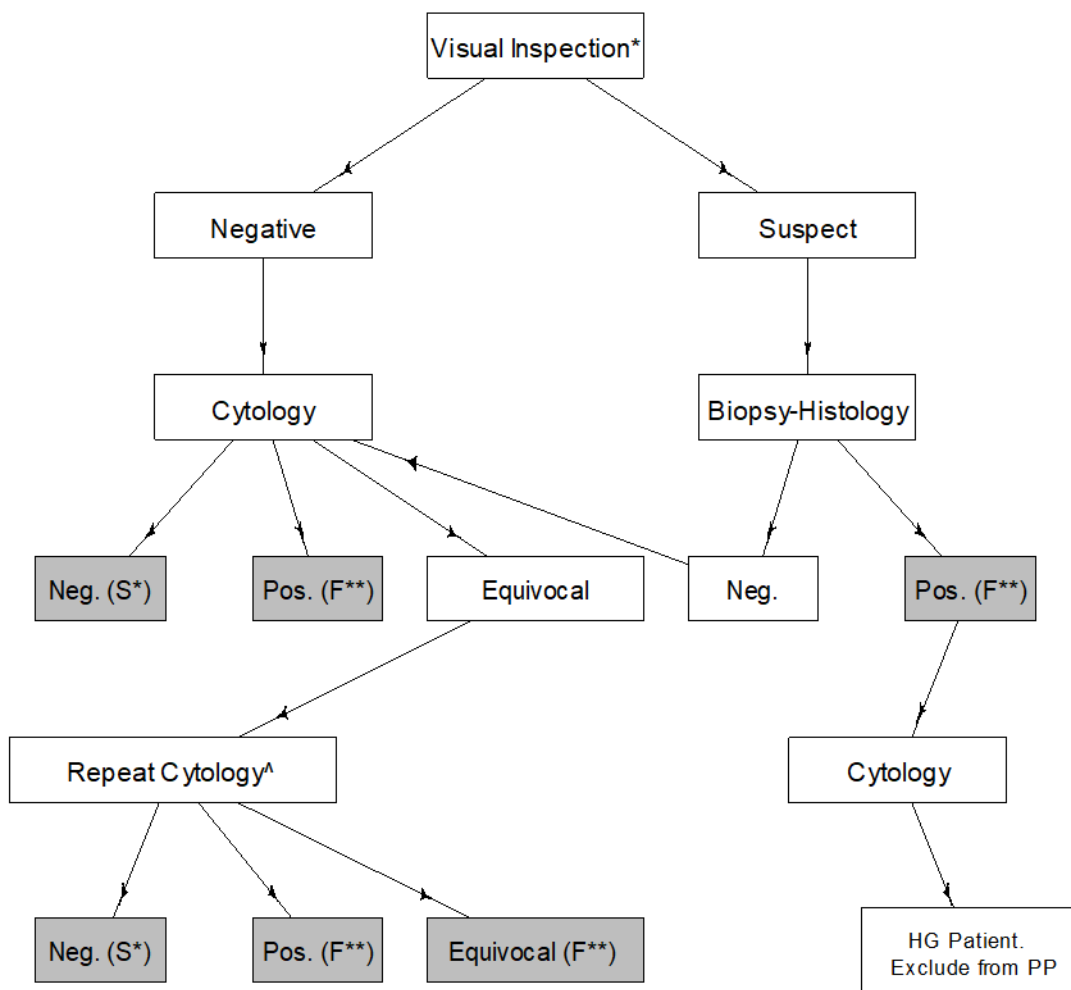
8.1.1.2. Study Endpoints

The Applicant's Description:

This study measured common and accepted measures of efficacy in oncology studies including the rate of CR (complete ablation of tumor lesions), rates of durability of CR, as well as changes in the size, location, number, and morphology of lesions. 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.

The primary efficacy endpoint was the proportion of patients attaining CR (ie, no detectable disease [NDD]; a complete ablation of tumor lesions as a response to the chemotherapy treatment), which was assessed during the PDE Visit. The PDE occurred at the pre-scheduled visit for endoscopic management treatment, scheduled for 5 weeks ($\pm$ 1 week) following the last instillation (approximately 3 months from Baseline). The key secondary efficacy endpoint was durability of CR at 12 months for patients who demonstrated CR at the PDE Visit. According to the literature, the recurrence rate is very high (50%-90%) at 6 months after a laser fulguration in the urinary tract for lesion removal. This endpoint was chosen to demonstrate that the CR result is durable over the course of a year.

Figure 3 Method for Determining Complete Response



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

Definitions:

- a. The CR was defined dichotomously as “Success” if CR was confirmed at PDE Visit (or relevant follow-up) and “Failure” otherwise (see Figure 3). A patient was considered to have had a CR if there was NDD.
- b. To determine NDD, the following conditions were to be fulfilled:
 - a. If visual assessment (ureterorenoscopy [URS]) indicated no remaining tumors, the upper tract urine cytology must have been negative.
 - b. If tumors were visible during URS, all remaining and accessible tumors were biopsied and evaluated by a local and a central pathologist. If the biopsied tumors were not

viable upon histopathological evaluation and the cytology was negative, the patient was considered to have CR.

- c. In cases where a patient underwent RNU for any reason, and the pathological evaluation indicated that no viable tumor(s) remained in the affected kidney (eg, non-viable lesion), the patient was considered CR retroactively.
- c. A patient was considered to have no complete response (NCR) if there was a residual disease. The NCR was determined only after pathology results were received from the pathology local lab.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the primary and key secondary endpoints for Study UT001. The primary endpoint was rate of CR at the PDE visit. The general principle for CR determination, to include no evidence of disease on uretosopic visualization, upper tract wash urine cytology, as well as biopsy for all lesions, if technically feasible, warranted and performed, was discussed and agreed upon with the FDA at the preIND meeting held June 1, 2015. Of note, investigator-assessed response may be subject to bias. In Study UT001, local cytology and biopsy results were used to determine CR and durability of complete response. All cytology and histopathology samples were also intended to be sent for central pathology review (b) (4).

Multiple classification systems exist for interpretation of urine cytopathology, of which the most widely used is the Paris classification system (Barkan et al; Acta Cytol 2016). The Paris System, which is primarily intended to detect high-grade urothelial carcinoma, includes the following diagnostic categories for reporting urine cytology:

1. Nondiagnostic/unsatisfactory
2. Negative for high-grade urothelial carcinoma (NHGUC)
3. Atypical urothelial cells (AUC)
4. Suspicious for high-grade urothelial carcinoma (SHGUC)
5. High-grade urothelial carcinoma (HGUC)
6. Low-grade urothelial neoplasm (LGUN)
7. Other: primary and secondary malignancies and miscellaneous lesions.

While the central pathology laboratory for Study UT001 exclusively reported results using the Paris System, the local laboratories on which the CR determination was based used a variety of classification systems, including Paris, the older Bethesda System, as well as other less common classification tools. Interpretation of cytology was not clearly pre-specified in the UT001 protocol and ultimately, determination of CR was based on each investigator's assessment of the local results. Additionally, the definition of what constituted an 'equivocal' urine cytology

was not provided in the protocol.

While the role of cytology in evaluation of LG-UTUC is controversial, given both limited sensitivity and specificity of cytology in this setting (McCroskey et al; Am J Clin Pathol 2015), the FDA reviewers do not consider the per-protocol assessment of CR to be adequately pre-specified. The FDA requested verbatim cytology reports from both local and central laboratories for all patients reported by the Applicant to have achieved complete response and manually reviewed all reports. While 'atypical urothelial cells' are not necessarily negative and do not exclude malignancy, cellular atypia are common with instrumentation and inflammation of the upper urinary tract, and FDA reviewers considered this to be a negative cytology. For the purpose of the review, a result of 'suspicious for high-grade urothelial carcinoma' was considered to be a positive cytology. See also discussion in Section 8.1.2.8.

With regards to duration of response, the FDA considered a response lasting at least 12 months from initial determination of response to be clinically meaningful in the setting of LG-UTUC for which the alternative therapy would likely be RNU.

Of note, protocol-mandated assessments continued only to the 12-month post-PDE visit. Methods of assessment of durability of response subsequent to the 12-month visit were at the discretion of the investigator and did not include central pathology review. Assessment of durability beyond 12 months may therefore be less reliable than during the protocol-mandated treatment and maintenance period.

8.1.1.3. SAP and Amendments

The Applicant's Description:

The SAP was agreed upon and finalized prior to the locking of the database.

Efficacy Statistical Methodology

Sample size determination was performed under the assumptions that the primary efficacy endpoint of the study was the proportion of CR rate at the PDE Visit, that it was expected that the true CR rate following treatment with UGN-101 is 30% or more, and that the primary analysis of the primary endpoint aimed to rule out a threshold rate of 15% using a 2-tailed test for binomial proportion at 2-sided $\alpha = 0.05$; ie, 15% CR was the performance goal of the study.

Under these assumptions, a sample size of 74 evaluable patients would provide a power of 88.5% to demonstrate that the observed CR rate was superior to the performance goal of 15%.

The primary efficacy analysis was performed using the ITT Analysis Set and tested the following hypothesis using an exact binomial 2-sided hypothesis testing, with 2-sided $\alpha = 0.05$. (Note that this was identical to the one-sided test with $\alpha = 0.025$):

Null hypothesis (H_0): CR rate at PDE $\leq 15\%$

Alternative hypothesis (H_1): CR rate at PDE $> 15\%$

Assuming the sample included 74 evaluable patients (the sample size planned in the protocol), the decision rule was to reject the null hypothesis above if the number of CRs in the sample was at least 18. If the number of evaluable patients was not 74, the rejection area was to be updated accordingly, using the same statistical methodology. The number and percentage of patients who were complete responders at PDE (with a 95% exact CI) and exact binomial hypothesis testing p-value were presented as a part of the primary efficacy analysis.

The key secondary endpoint was durable response at the 12-month follow-up post PDE Visit which tested the following hypothesis based on Kaplan-Meier time-to analysis.

H_0 : CR rate at 12 months $\leq 40\%$

H_1 : CR rate at 12 months $> 40\%$

Success for this endpoint was declared if the lower bound of the 95% CI for durability of tumor ablative effect at 12 months was $> 40\%$. In addition, a Kaplan-Meier survival plot and quartiles and median durability of tumor ablative effect with the corresponding 95% CI were presented. The supportive analysis using dichotomous long-term durability of CR included the frequency distribution of dichotomous observed long-term durability of CR, along with exact 95% CI.

Subgroup analysis for the primary endpoint (ITT Analysis Set) and for the key secondary endpoint (PDE_{CR} Analysis Set) examined potential effects on the primary and key secondary (continuous) endpoints.

Safety Statistical Methodology

All safety analyses were based on the safety population which consisted of all subjects who received at least one dose of the study treatment. Subject data were analyzed according to the treatment actually received. Separate AE summaries were presented by system organ class (SOC) and preferred term (PT). All AEs, Grade 3-4 AEs, treatment-related AEs, serious AEs (SAEs), AEs leading to discontinuation, and adverse events of special interest (AESIs) were summarized. Laboratory data including worst post-baseline results and vital signs were also

provided. Safety summary tables included “treatment-emergent” events/assessments (ie, those collected on or after the first date of study treatment).

The FDA’s Assessment:

FDA reviewed the SAP prior to submission of this NDA and found it to be acceptable, but notes the following:

1. In single arm trials, FDA does not use inferential procedures to evaluate trial results. Instead, the efficacy evaluation is based on the magnitude of the proportion of CR rate at the PDE Visit and adequate response durability.
2. Kaplan-Meier estimates of durability may be misleading if the follow-up data are immature. Since duration of CR is not mature, FDA computes the percentage of responding patients who remained in CR at the 12-month post-PDE visit without regards to censoring.

8.1.1.4. Protocol Amendments

The Applicant’s Description:

Protocol Version 4.0 was the first version to be approved and distributed to site, so previous versions have not been included in the appendix or referenced in the clinical study report (CSR). The following important changes were implemented via protocol amendment:

1. Trial objectives were updated: Classified efficacy objectives as Primary, Key Secondary, and Secondary. Response durability at 12-month follow-up for patients showing CR at PDE visit, previously an exploratory objective, became the Key Secondary Objective.
2. Clarified endpoints: All possible scenarios for scoring the primary endpoint CR, “success” or “failure,” were clarified. Specified hypothesis testing for the key secondary endpoint, durability of CR at 12-month post-PDE Visit by exact binomial CI, and described a Kaplan-Maier analysis for durability of CR at 12-month post-PDE Visit.
3. Updated analysis populations: Specified that ITT, determined by local (rather than central) histology, is the Primary Analysis Set (ie, for the primary endpoint); Changed the modified ITT (mITT) Analysis Set to secondary and was based on observed data only for patients diagnosed as LG by the central laboratory; Central mITT Analysis Set was added.
4. Updated eligibility criteria, clarified patient eligibility review and enrollment, and updated the Evaluation plan at follow-up to include an option for data collection up to 3 years post PDE-visit.

The FDA’s Assessment:

FDA generally agrees with the applicant's description of the key protocol changes. The primary analysis population included all patients who received at least one treatment instillation. FDA notes that Kaplan-Meier estimates of durability may be misleading if the follow-up data are immature. Since duration of CR is not mature, FDA computes the percentage of responding patients who remained in CR at the 12-month post-PDE visit without regards to censoring.

While the Applicant states that all possible scenarios for scoring the primary endpoint CR "success" or "failure" were clarified, FDA notes that detailed interpretation of cytology results as a component of CR were not pre-specified in any version of the protocol.

The FDA does not consider any of the implemented changes to have impacted the integrity of the trial or the interpretation of the results.

8.1.2. Study Results

The study start date (date of first center initiation) was 30 Jan 2017. The first patient was enrolled on 04 Apr 2017. The data cutoff date for this analysis and report was 22 May 2019.

8.1.2.1. Compliance with Good Clinical Practices

The Applicant's Position:

The study was performed in accordance with the US FDA Good Clinical Practice (GCP) Regulations (Code of Federal Regulations [CFR] 21 parts 50, 56, and 312), International Conference on Harmonization GCP Guidelines (E6), and clinical safety data management (E2A).

A written informed consent form (ICF), in compliance with 21 CFR Part 50, was obtained from each patient prior to enrollment and Screening evaluations. A copy of the ICF was reviewed by the Sponsor (or designee) for acceptability, then submitted by the Investigator to the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) for review and approval prior to the start of the study. Consent forms were required to be in a language fully comprehensible to the prospective patient. The Investigator provided the Sponsor (or designee) with a copy of the IRB/EC letter approving the study protocol and the ICF(s) before the study drug supplies were to be shipped and the study initiated.

The written ICF was to be revised if new information became available during the study that was relevant to the patient. Any revisions were to be submitted to the appropriate IRB/EC for review and approval in advance of use. It was the responsibility of the Investigators (or representatives) to obtain the informed consent of all patients after giving them sufficient information regarding the objectives, methods, expected benefits, and foreseeable risks of the study. The Investigators (or representatives) also informed patients that they may choose not to participate in the study, or discontinue participation for any reason, without penalty.

The FDA's Assessment:

FDA agrees with the Applicant's assessment above.

8.1.2.2. Financial Disclosure

The Applicant's Position:

Details of financial disclosure are presented in Section 19.2.

The FDA's Assessment:

The Applicant has disclosed that one principal investigator, (b) (6) has an ongoing financial arrangement with the Applicant, as a consultant to UroGen's (b) (6) program specifically focusing on (b) (6). Refer to FDA's Assessment of Section 19.2.

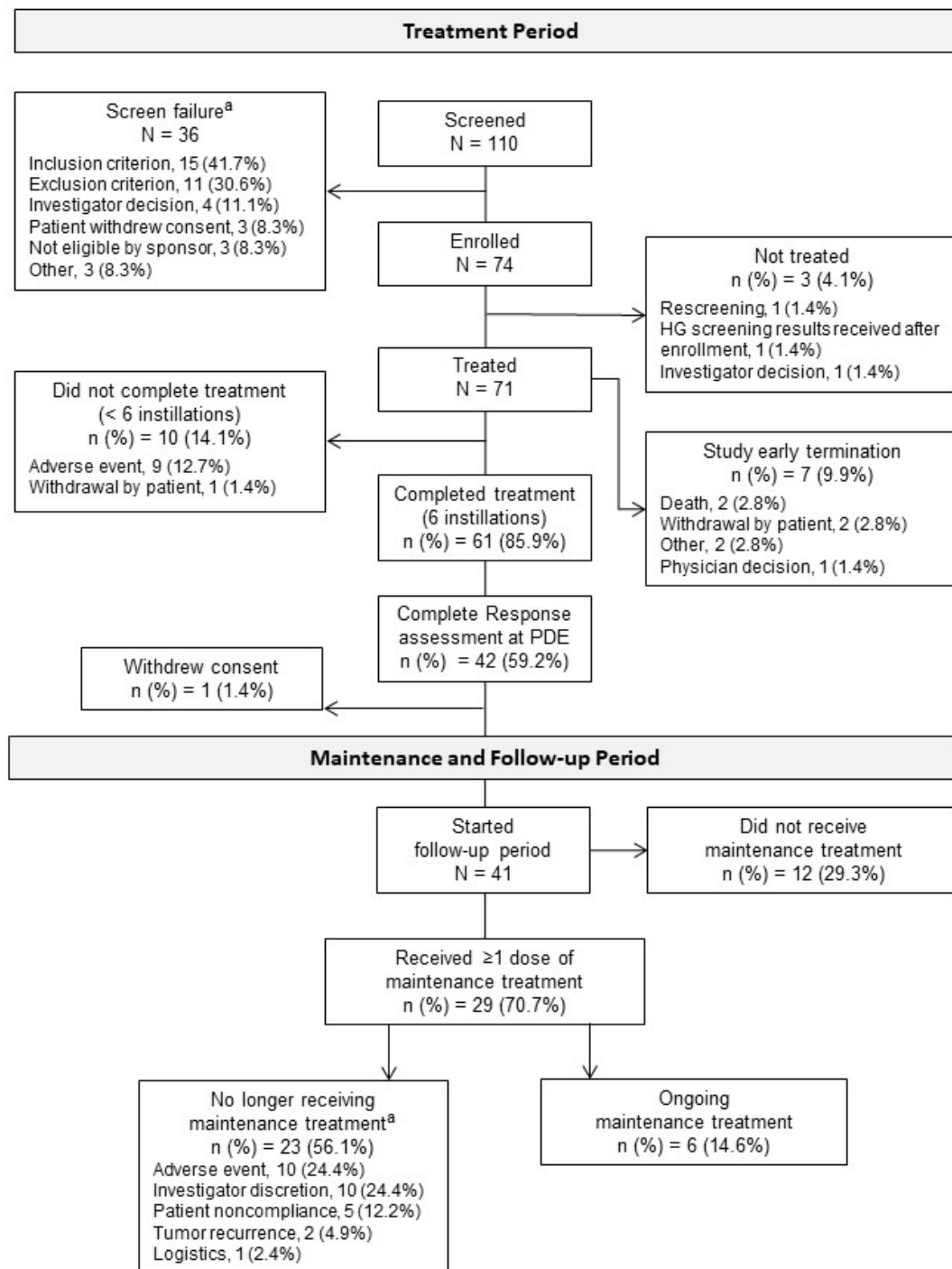
8.1.2.3. Patient Disposition

The Applicant's Position:

A total of 74 patients were enrolled, and 71 patients received at least 1 treatment instillation. Of these treated patients, 61 (85.9%) patients completed treatment per protocol, 48 (67.6%) patients completed the study per protocol at the time of data cutoff for the CSR, and 16 (22.5%) patients remained in follow-up at the time of the data cutoff. The main reason for early treatment termination was AEs (9 [12.7%] patients), and 1 (1.4%) patient withdrew early by their own decision. None of the reasons for study early termination were reported by more than 2 patients. Of note, there were 3 deaths in the study but only 2 were documented as leading to study early termination.

Of the 42 patients who met criteria for maintenance treatment and follow-up period, 41 patients started the follow-up period, and 29 (70.7%) patients received ≥ 1 dose of maintenance treatment. A total of 6 (14.6%) patients were receiving maintenance treatment at the time of the data cutoff.

Figure 4 Disposition of Patients



a. More than 1 reason was possible.

Source: Table 14.1.3, Table 14.1.4, Listing 16.2.1.2

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of patient disposition.

Ten patients enrolled in the initial Treatment Period of UT001 did not complete all six treatments. The reasons for discontinuation of treatment were adverse events (9 patients) and withdrawal of consent by patient (1 patient). The adverse events leading to early termination in the Treatment Period were:

- Ureteric Obstruction (5 patients)
- Bone marrow toxicity (2 patients)
- Renal Dysfunction (2 patients)
- General physical health deterioration (1 patient)

While 42 patients were eligible for maintenance treatment, 41 patients started the maintenance period of the study. One patient withdrew consent and did not continue maintenance period of the study. Of the 41 starting the maintenance period, 29 patients received one or more instillations of maintenance therapy. Twelve patients entered the maintenance period, but did not receive treatment. The reasons for discontinuation prior to receiving maintenance therapy are:

- Death (4 patients)
- Other (4 patients)
- Investigator discretion (2 patients)
- Patient withdrawal of consent (2 patients)

8.1.2.4. Protocol Violations/Deviations

The Applicant's Position:

Protocol deviations were identified prior to database lock. A total of 46 (64.8%) patients had at least 1 major protocol deviation: 28 (39.4%) relating to patient management, 25 (35.2%) relating to study conduct, and 3 (4.2%) relating to patient eligibility.

Several protocol deviations were later permitted by subsequent protocol amendments. No patients were excluded from any analysis set due to a protocol deviation.

The FDA's Assessment:

Review of patient eligibility violations in UT001 did not identify those that may have impacted study results. One patient (b) (6) had a screening cytology read as "suspicious for high-grade disease" but a subsequent specimen was read as consistent with low-grade disease. Two other patients had missing cytology or a biopsy outside of the screening window. (Table 8)

In addition, 17 patients had protocol deviations / violations involving cytology or biopsy. Details regarding deviations are as follows:

- Missing Data: 11 patients
- Collection of sample(s) performed outside of protocol-specified time window: 6 patients.
- Patient (b) (6). Screening local lab cytology was 'suspicious to HG' (did not meet inclusion criterion #7) but was approved by the sponsor since local pathology result showed LG disease and following consultation
- Patient (b) (6). Screening UUT Cytology and UUT Biopsy for Histopathology (Central Lab Results): Subject was enrolled onto study with these samples being shipped and processed by the central lab.
- Patient (b) (6). The Repeated cytology (screening visit) was obtained but the lab misplaced the samples and could not be analyzed
- Patient (b) (6). FU4: multiple analytes were not done for renal and liver function, PT was not done for coagulation, urinalysis/dipstick lab tests were not done. Cytology sample was voided urine and not upper tract
- Patient (b) (6). Screening local biopsy confirming LG (b) (6) is over 8 weeks prior to screening visit. Protocol 4.0 inclusion wording is the same as shown here. The limitation of 8 weeks is written in the study
- Patient (b) (6). On (b) (6), patient came in to his MT3 treatment along with FU1 and in biopsy test a recurrence of the tumor was seen. Therefore, patient completed the study and was supposed to come one month after

Table 8. Summary Protocol Violations / Deviations, Study UT001

Protocol Deviation	Number of Patients n=71 (%)
Patient Eligibility	12 (17%)
Lab criteria not met	13 (18)
Cytology or Biopsy Issues	3 (4.2)
Patient Management (Major only)	28 (39)
Study Conduct (Major only)	25 (35)
Source: dv.xpt, suppdv.xpt	

Many of these violations were related to missing slides/samples that were intended to be sent for central laboratory review. This did not significantly impact the FDA’s review of cytology discussed in 8.1.1.2, however as there were no cases in which the local laboratory result was read as ‘suspicious for high-grade disease’ but the central laboratory result was missing. One patient ((b) (6)) had a voided urine cytology sample taken, instead of UT wash cytology at Follow-Up Visit 4 (12-month post-PDE visit). This patient should also be considered to have a missing cytology result for this time period. A missing cytology sample at the PDE visit for Patient (b) (6) , was retrospectively determined to be in CR following a negative cytology result at the 3-month follow-up visit.

Sensitivity analyses considering the above protocol violations or deviations as treatment failures at the time of violation did not sufficiently affect the risk/benefit profile of UGN-101 for the treatment of LG-UTUC to change the overall recommendation for approval.

Major protocol deviations relating to patient management and study conduct were also reviewed. While a large proportion of patients experienced a major deviation, most were related to regulatory (missing informed consent signature or incorrect version, late SAE reporting) or minor study conduct issues, including staying for less than the recommended post-instillation observation window. Ten patients had missing labs that could potentially have impacted incidences of safety outcomes. Three patients were treated with a greater volume of product than pre-specified. Overall, these deviations did not appear to affect interpretation of the study results.

8.1.2.5. Table of Demographic Characteristics

Table 9 Demographic Characteristics of the Primary Efficacy Analysis (Study UT001 – ITT Analysis Set)

Summary of Baseline Characteristics	N = 71
Age (years)	n = 71

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Summary of Baseline Characteristics	N = 71
Mean (SD)	70.4 (10.0)
Median (Min, Max)	71.0 (42.0, 87.0)
Age group (years), n (%) ^a	
Age < 65	18 (25.4)
65 ≤ Age < 75	27 (38.0)
Age ≥ 75	26 (36.6)
Weight (kg)	n = 71
Mean (SD)	83.5 (18.3)
Median (Min, Max)	82.1 (40.8, 132.9)
Height (cm)	n = 71
Mean (SD)	171.3 (10.6)
Median (Min, Max)	171.0 (152.0, 191.0)
BMI (kg/m ²)	n = 71
Mean (SD)	28.4 (5.6)
Median (Min, Max)	27.9 (17.0, 47.7)
BMI group (kg/m ²), n (%) ^a	
BMI ≤ 30	47 (66.2)
BMI > 30	24 (33.8)
Sex, n (%) ^a	
Male	48 (67.6)
Female	23 (32.4)
Race, n (%) ^a	
Caucasian	62 (87.3)
African American	4 (5.6)
Hispanic	3 (4.2)
Asian	2 (2.8)
Other	0 (0.0)

BMI = body mass index, ITT = intent-to-treat.

1. Percentage was calculated from the overall number of patients in the ITT Analysis Set.

Source: Table 14.1.6.

The Applicant's Position:

The enrolled population represented the intended patient population with respect to age and co-morbidities. Complete demographic information was collected at baseline for all treated patients.

The FDA's Assessment:

FDA generally agrees with the applicant's presentation of demographic information. The study population consisted of 71 patients of which 67.6% were males and 32.4% were females. The median age was 71 years (range: 42-87 years). The majority of the patients (87.3%) were Caucasian.

Overall, the demographics of the patient population is consistent with the SEER database for UTUC with 62% male and 92% white (JJ Munoz et al. Journal of Urology 2000).

8.1.2.6. Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

At baseline, the majority of patients were either current or past smokers (21 [29.6%] and 35 [49.3%] patients, respectively) with good level of daily functioning ((b) (4) performance score of 0 = 50 [70.4%] patients; Karnofsky score of 100 = 43 [60.6%] patients), which is representative of the real-world patient population.

This older population had substantial baseline morbidity. The most common non-UC conditions by PT ($\geq 25\%$ patients) were Hypertension (47 [66.2%] patients), Hyperlipidemia (35 [49.3%] patients), Gastroesophageal reflux disease (25 [35.2%] patients) and Benign prostatic hyperplasia (18 [25.4%] patients). A large proportion of patients had a history of at least 1 prior episode of UC (43 [60.6%] patients) and 34 (47.9%) patients had at least 1 prior episode of UUT. In addition, there were 8 (11.3%) patients with only 1 kidney.

Current UUT Episode at Time of Study Enrollment

Based on inclusion criteria, all patients were to have at least 1 measurable papillary LG tumor, evaluated visually, size ≤ 15 mm, located above the ureteropelvic junction (UPJ). Post-debulking, lesion size was required to be ≥ 5 mm. The number and size of papillary lesions (prior to debulking, if applicable) for the current UUT episode were summarized. The mean number of papillary lesions was 2.2 and the number ranged from 1 to 8 per patient. The mean diameter of the largest papillary tumor was 14.8 mm and the range was 5 to 50 mm. The total tumor burden was 19.9 mm and the range was 5 to 65 mm.

Close to half of all patients (47.9%) had tumors that were unreachable by laser (ie, endoscopically unresectable). Reasons for tumors being considered endoscopically unresectable were recorded retrospectively by sites in a comments field of the CRF and included location of tumor/anatomical reasons, poor visualization, and size.

The FDA's Assessment:

The FDA agree with the Applicant's assessment of baseline disease characteristics. The post-debulking tumor burden may be meaningful as patients with lower baseline tumor size may be more likely to have a complete response after local therapy. The median number of papillary lesions immediately prior to treatment was 1 (range: 1, 5), the median diameter of the largest lesion was 8mm (range: 5, 15), and the total tumor burden was 10mm (range: 5, 25).

A total of 48% of patients had tumors that were considered endoscopically unresectable, which was recorded retrospectively. Contraindications for alternative therapies, including RNU, were not otherwise specifically recorded, although 11% of patients had a single kidney, which is a relative contraindication to RNU. Sixty-one percent of patients had a prior urothelial carcinoma episode including 48% with at least one prior upper urinary tract episode. In terms of prior procedures and therapies related to urothelial carcinoma, the CRF did not distinguish between upper tract and bladder procedures, however 52% percent of patients had undergone prior kidney ablation.

Sixteen patients (22.5%) received prior chemotherapies, including mitomycin, gemcitabine, thiotepa, or epirubicin, and 9 patients (12.7%) received prior bacilli Calmette-Guerin exposure, although it was not recorded whether these were intravesical or intraureteral therapies.

8.1.2.7. Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

The majority of patients, 61/71 (85.9%) received all 6 instillations during the treatment period. Compliance in the maintenance phase was less consistent, in part due to investigators' clinical decisions to change dosing frequency in the maintenance regimen. Per the protocol, patients who were CR at PDE were to continue on to receive monthly maintenance instillations for 11 doses or until they demonstrated a recurrence. In practice, Investigators significantly modified maintenance regimens based on a number of factors (eg, patient preference, adverse effects, and patient comorbidity). In both the ITT and PDE_{CR} analysis sets, the median number of instillations during both the treatment and maintenance period was 6 at the time of data cut off (maintenance period is still ongoing).

The majority of patients complied with sodium bicarbonate intake the night prior to and the morning of treatment. The lowest compliance was observed at 30 minutes prior to instillation procedure, in most cases due to the restrictions associated with general anesthesia. Mean compliance overall was 90.8% during the treatment period and 80.4% during the maintenance period.

The majority of patients complied with prophylactic antibiotics during the treatment and maintenance periods. A small proportion of subjects did not receive prophylactic antibiotics per

Investigator decision. Mean compliance with prophylactic antibiotic taken pre-treatment was 92.2% during the treatment period and 95.8% during the maintenance period.

The majority of patients did not receive general anesthesia during instillation in the treatment period. The number (%) of patients in the ITT analysis set receiving general anesthesia ranged from 14/71 (19.7%) to 21/71 (29.6%) across the instillations in the treatment period. Higher percentages of patients received anesthesia during the maintenance period compared with the treatment period because they underwent URS at the 3-, 6-, 9-, and 12-month follow-up post-PDE Visit, while they only underwent URS once during the treatment period (at the PDE visit). Feedback during protocol development and study startup originally assumed that all patients would require general anesthesia to tolerate the retrograde instillation of UGN-101. The practical experience was that anesthesia was required only by a limited number of patients. Patients also reported feeling generally low pain levels during the UGN-101 instillation (the median at each instillation ranged from a score of 9 to 10 mm on a 100 mm scale), and only 1 patient could not proceed with instillation due to pain.

Concomitant Medication

As expected for an elderly population with significant comorbidities, the majority of patients required concomitant medication unrelated to UC. In addition, the most common (≥ 5 patients) concomitant procedures and surgeries included ureteral stent insertion (36 [50.7%] patients), ureter dilation procedure (10 [14.1%] patients), and transurethral bladder resection (6 [8.5%] patients). No patient received any prohibited medication during the study.

Rescue Medication

Not applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of treatment compliance. The majority of patients (86%) received 6 instillations in the treatment period. General anesthesia was administered at the discretion of the investigator and was used for 28% of all instillation across both Treatment and Maintenance periods. In the Treatment Period, general anesthesia was administered for 24% of instillations, while general anesthesia was administered for 37% of instillations in the Maintenance Period (Table 10). In terms of any requirement for general anesthesia, general anesthesia was used in 37% of patients for at least one instillation during the Treatment Period and for 61% of patients for at least one instillation during the follow-up period. Analysis of rate of general anesthesia by instillation number did not reveal any clear trend toward greater use of general anesthesia with greater cumulative number of instillations, however patients with adverse events related to instillation may have discontinued earlier in the study. The use of general anesthesia does carry significant risk, however is commonly used during endourological procedures including alternative therapies such as endoscopic resection.

Table 10 Use of General Anesthesia, Study UT001

	<u>Patients receiving</u>	<u>Use of General Anesthesia</u>	
<u>Instillation Number</u>		<u>Yes</u>	<u>No</u>
	<u>Treatment Period; n=71 (%)</u>		
Treatment 1	71 (100)	21 (30)	50 (70)
Treatment 2	71 (100)	15 (21)	56 (79)
Treatment 3	71 (100)	14 (20)	57 (80)
Treatment 4	70 (99)	17 (24)	54 (76)
Treatment 5	69 (97)	17 (24)	53 (76)
Treatment 6	61 (86)	18 (28)	46 (72)
	<u>Maintenance Period; n=41 (%)</u>		
Maintenance Treatment 1	28 (68)	10 (32)	21 (68)
Maintenance Treatment 2	25 (61)	5 (19)	22 (81)
Maintenance Treatment 3	20 (49)	14 (56)	11 (44)
Maintenance Treatment 4	17 (41)	14 (50)	10 (50)
Maintenance Treatment 5	16 (39)	7 (37)	12 (63)
Maintenance Treatment 6	12 (29)	8 (53)	7 (47)
Maintenance Treatment 7	11 (27)	6 (43)	8 (57)
Maintenance Treatment 8	8 (20)	3 (30)	7 (70)
Maintenance Treatment 9	8 (20)	4 (33)	8 (67)
Maintenance Treatment 10	4 (10)	1 (14)	6 (86)
Maintenance Treatment 11	4 (10)	2 (29)	5 (71)

Source: pr.xpt

8.1.2.8. Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Results of the primary evaluation of response at the PDE Visit are summarized in Table 8. A significant majority of patients were complete responders at the PDE Visit, 42 (59.2%) patients (95% CI: 46.8, 70.7; $p < 0.0001$), as determined by the exact binomial test versus the prespecified performance goal of 15%. The classifications of response for the 29 (40.8%) patients with no CR included: NR (12 [16.9%] patients), PR (8 [11.3%] patients), presence of HG disease not identified at baseline (6 [8.5%] patients), and indeterminate response (3 [4.2%] patients).

Table 11 Primary Disease Evaluation

Parameter/Summary	n (%) ^a
Local laboratory PDE (ITT, N = 71)	
Complete response	42 (59.2)
No complete response:	29 (40.8)
Partial response	8 (11.3)
No response	12 (16.9)
High grade patient	6 (8.5)
Indeterminate ^b	3 (4.2)
Total	71 (100.0)

CRF = case report form, ITT = Intent-to-Treat, PDE = primary disease evaluation.

^a For local lab results, percentage was calculated from the overall number of patients in the ITT analysis set; for central lab results, percentage was calculated from the overall number of patients in the Central - mITT analysis set.

^b Indeterminate patients were those who had 'undetermined' (or 'not done') on CRF form 'Evaluation of Response (Target Area Lesions)' at PDE and at re-evaluation, or had no re-evaluation. For the primary analysis these patients are considered as 'non-complete responders'.

Source: Study UT001 CSR Table 14.2.1.

Sensitivity analyses repeating the primary analysis in additional analysis sets demonstrated similar rates of CR. In addition, central laboratory results confirmed the local laboratory evaluation.

Subgroup and response-by-dose analyses were also completed. Homogeneity and consistency of the treatment effect was evident across major demographic, baseline disease characteristics, and extent of treatment subgroups. However, total tumor burden (pre-debulking) seemed to have a small effect on CR at the PDE Visit. Patients with a smaller pre debulking tumor burden (≤ 17 mm) had a higher CR rate (24 out of 34 patients [70.6%]), than those with a larger tumor

burden (> 17 mm; 14 out of 32 patients [43.8%]) (Study UT001 CSR Table 14.2.15). In addition, by-site analysis of patients at the 2 highest enrolling study sites demonstrated discordant response rates. Patients enrolled at Sheba Medical Center Tel Hashomer Hospital, a large community hospital, had a CR rate of 9 out of 13 patients (69.2%); while patients enrolled at MD Anderson, a tertiary care institution, had a CR rate of 2 out of 9 patients (22.2%) (Study UT001 CSR Table 14.2.16). A comparison of baseline characteristics for these 2 sites, each of which enrolled > 10% of the study population, showed that pre- and post-tumor debulking tumor burden at Screening appeared to be higher for patients at MD Anderson (Study UT001 CSR Table 14.2.18). This is consistent with the findings from the overall predebulking tumor burden subgroup analysis and may have impacted the evaluation of efficacy at PDE.

The FDA's Assessment:

The FDA disagrees with the primary efficacy evaluation methodology, specifically interpretation of cytology results (see Section 8.1.1.2). FDA analysis identified issues with two patients who were classified as CR, one which impacted the primary efficacy endpoint of CR at PDE, and one which impacted the secondary endpoint of durability of CR.

Patient (b) (6) had a local and central lab read as “suspicious for high-grade disease” and thus residual disease could not be excluded at the PDE visit. This patient is considered non-CR despite the negative ureteroscopy at this time point.

Patient (b) (6) 1 had a FU2 visit cytology read as “suspicious for high-grade disease” by both local and central laboratories and is considered to have recurred at that time point.

OSI investigation of Site 16 identified three patients ((b) (6)) for which they report that urine cytology reports were questionable for the reported CR per the study protocol definition. As noted in Section 8.1.1.2, the FDA clinical review team closely reviewed the verbatim local and central pathology records for these three patients. For these three patients, the clinical reviewers determined that the central pathology result did not indicate the presence of LG-UTUC and these patients were considered to have achieved a CR. As previously noted, atypical cells in the setting of a negative ureteroscopy were considered a negative result by the FDA, although the protocol did not pre-specify this interpretation. Cytology has limited utility for the detection of LG-UTUC given the rare presence of fibrovascular cores, which are generally required for diagnosis, and the primary goal of classification systems including the Paris System are to detect high-grade malignancy. Atypia are commonly related to instrumentation and/or inflammation, carry a pre-test probability of high-grade malignancy of 8-35% and, in the absence of other findings indicative of persistent or recurrent disease, is typically managed with routine follow-up similar to a true negative (Barkan et al, Acta Cytol

2016). However, the lack of adequate pre-specification of cytology interpretation is a major limitation of Study UT001.

Based on the revised assessment, 41 (58%) patients (95% CI: 45%, 69%) were complete responders by the local laboratory evaluation at the PDE Visit.

In single arm trials, FDA does not use inferential procedures to evaluate trial results. The p-value reported in this section is not appropriate.

The discordance rate between the local and central laboratory was 16.9% (Table 10) and is acceptable for CR assessment in a single arm study.

Table 12: Discordance rate of complete response assessment between local and central laboratory

		Central Laboratory		Discordance Rate
		Complete Response	No complete response	
Local Laboratory	Complete Response	33	8	16.9%
	No complete response	4	26	

Source: Reviewer analysis using adrs.xpt datasets

Subgroup analyses were performed for the primary endpoint of CR rate (Table 13).

Table 13: Complete Response Rate by Baseline Characteristics (N=71)

Baseline Characteristics	N (%)	CR rate [n (%)]	95% CI
Age			
< 65	18 (25.4)	10 (55.6)	(30.8, 78.5)
65 – 74	27 (38.0)	16 (59.3)	(38.8, 77.6)
>= 75	26 (36.6)	15 (57.7)	(36.9, 76.6)
Sex			
Female	23 (32.4)	14 (60.9)	(38.5, 80.3)
Male	48 (67.6)	27 (56.3)	(41.2, 70.5)
Race			
African American	4 (5.6)	3 (75.0)	(19.4, 99.4)
Asian	2 (2.8)	1 (50.0)	(1.3, 98.7)
Caucasian	62 (87.3)	35 (56.5)	(43.3, 69.0)
Hispanic	3 (4.2)	2 (66.7)	(9.4, 99.2)
Country			

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Baseline Characteristics	N (%)	CR rate [n (%)]	95% CI
ISR	14 (19.7)	10 (71.4)	(41.9, 91.6)
USA	57 (80.3)	31 (54.4)	(40.7, 67.6)
Site			
Sheba Medical Center Tel Hashomer Hospital	13 (18.3)	9 (69.2)	(38.6, 90.9)
MD Anderson	9 (12.7)	2 (22.2)	(2.8, 60.0)
Debulking at Baseline			
Yes	51 (71.8)	30 (58.8)	(44.2, 72.4)
No	20 (28.2)	11 (55.0)	(31.5, 76.9)
Pre-Debulk Papillary Lesions Number			
1	34 (47.9)	18 (55.9)	(37.9, 72.8)
2	13 (18.3)	9 (69.2)	(38.6, 90.9)
≥ 3	23 (32.4)	14 (60.9)	(38.5, 80.3)
Post-Debulk Papillary Lesions Number			
1	48 (67.6)	29 (60.4)	(45.3, 74.2)
> 1	22 (31.0)	12 (54.5)	(32.2, 75.6)
Pre-Debulk Largest Diameter (mm)			
≤ 10 mm	29 (40.8)	20 (69.0)	(49.2, 84.7)
> 10 mm	38 (53.5)	20 (52.6)	(35.8, 69.0)
Post-Debulk Largest Diam (mm)			
≤ 10 mm	57 (80.3)	35 (61.4)	(47.6, 74.0)
> 10 mm	13 (18.3)	6 (46.2)	(19.2, 74.9)
Pre-Debulk Tumor Burden (mm)			
≤ 17 mm	34 (47.9)	23 (67.6)	(49.5, 82.6)
> 17 mm	32 (45.1)	14 (43.8)	(26.4, 62.3)
Unknown	5 (7.0)	4 (80.0)	(28.4, 99.5)
Post-Debulk Tumor Burden (mm)			
≤ 10 mm	39 (54.9)	25 (64.1)	(47.2, 78.8)
> 10 mm	31 (43.7)	16 (51.6)	(33.1, 69.8)
Tumor is Unreachable by Laser			
Yes	34 (47.9)	20 (58.8)	(40.7, 75.4)
No	37 (52.1)	21 (56.8)	(39.5, 72.9)
Prior chemotherapy			
Yes	15 (21.1)	12 (80.0)	(51.9, 95.7)
No	56 (78.9)	29 (51.8)	(38.0, 65.3)
Prior BCG			
Yes	9 (12.7)	6 (66.7)	(29.9, 92.5)
No	62 (87.3)	35 (56.5)	(43.3, 69.0)
No. of Treatment Instillations Group			

Baseline Characteristics	N (%)	CR rate [n (%)]	95% CI
6	61 (85.9)	35 (57.4)	(44.1, 70.0)
< 6	10 (14.1)	6 (60.0)	(26.2, 87.8)
Number of Past UC Episodes			
0	28 (39.4)	15 (53.6)	(33.9, 72.5)
> 0	43 (60.6)	26 (60.5)	(44.4, 75.0)

Source: Reviewer analysis using adrs.xpt and adsl.xpt datasets

Higher response rates were seen in patients who were enrolled in Israel (71.4%) and who had a 10mm or less tumor burden post-debulking (if performed) immediately prior to treatment compared to a tumor burden >10mm (64% vs 52%) although we note these subgroups had wide confidence intervals due to small sample sizes. No outlier subgroups were otherwise observed. All subgroup analyses presented are considered exploratory, and no formal inference can be drawn.

8.1.2.9. Data Quality and Integrity

The Applicant's Position:

No data integrity concerns were reported following completion of site inspections. No for-cause audits were required and all pre-specified site audits were carried out as planned in the monitoring plan. One site did undergo a non-clinical hold due to identification of the need for staff retraining at a site audit.

The FDA's Assessment:

Clinical Inspection of Site 16 (Ahmad Shabsign, Ohio State University) resulted in an issuance of Form FDA-483 for two observations:

- 1) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation
- 2) An investigation was not conducted in accordance with the investigational plan

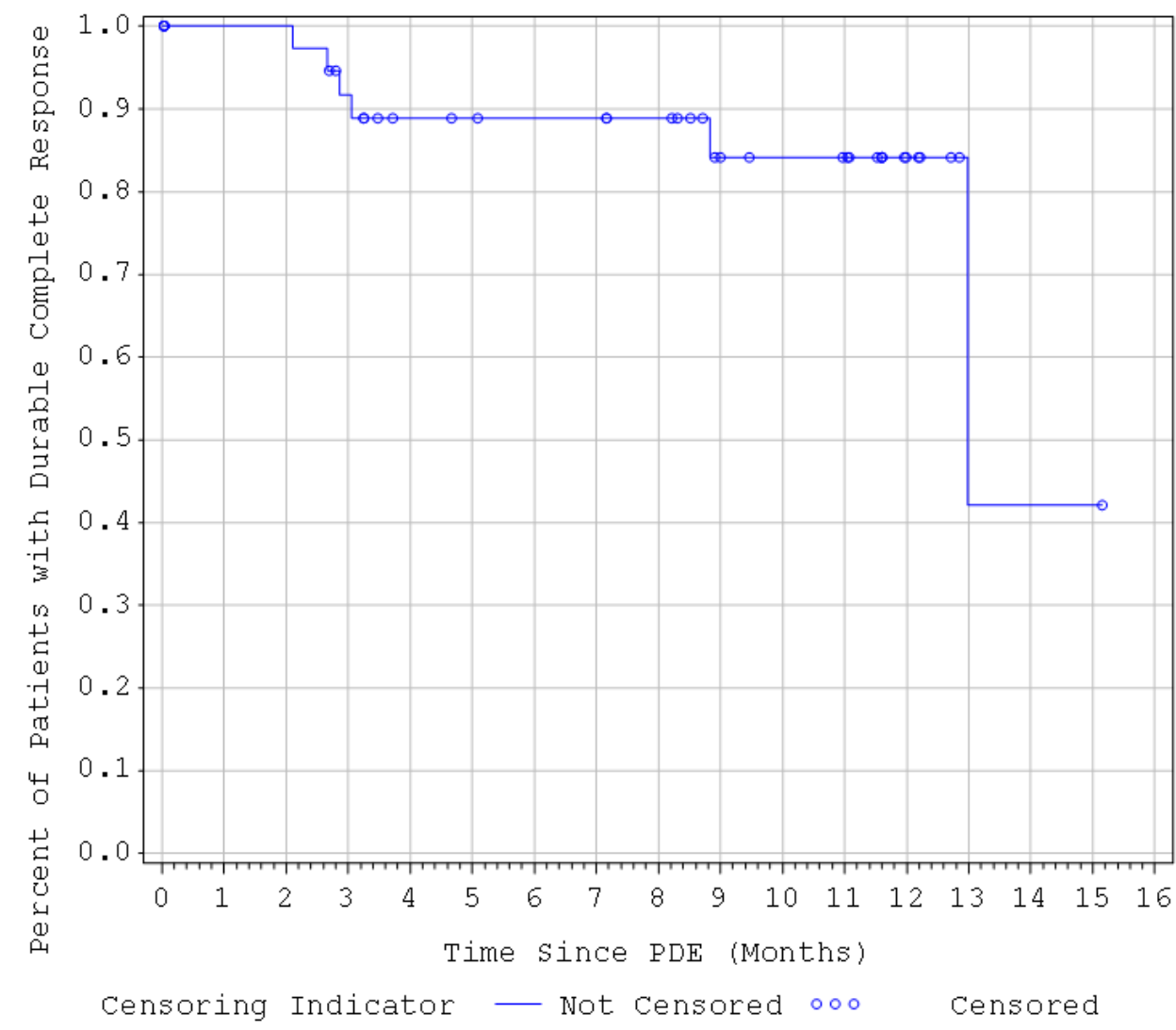
Refer to Section 4.1 for additional details regarding the Clinical Inspection.

8.1.2.10. Efficacy Results – Secondary and other relevant endpoints

Key Secondary Endpoint

A time-to-recurrence Kaplan-Meier plot illustrates that the effect of UGN-101 remained durable for the majority of patients who achieved CR at the PDE Visit (Figure 5). Durability of response was estimated at 84.2% (95% CI: 71.0, 97.4) at 12 months post-PDE Visit (Table 9), median time-to-recurrence was 13.0 (95% CI: 13.0, -) months (Study UT001 CSR Table 14.2.5).

Figure 5 Kaplan-Meier Curve of Durability of Response During the Maintenance Period (PDE_{CR} Analysis Set)



Source: Study UT001 CSR Figure 4

PDE = primary disease evaluation, PDE_{CR} = complete responders at the PDE visit.

Table 14 Kaplan-Meier Estimates for Durability of CR (PDE_{CR} Analysis Set)

Time Since PDE	N = 41	Percentage of Patients With Durable CR	
	N ^a	% (SE)	95% CI (%) ^b
1 month	37	100.0 (0.0)	(100.0, 100.0)
2 months	37	100.0 (0.0)	(100.0, 100.0)
3 months	35	91.7 (4.6)	(82.8, 100.0)
4 months	31	88.9 (5.3)	(78.6, 99.2)
5 months	30	88.9 (5.3)	(78.6, 99.2)
6 months	29	88.9 (5.3)	(78.6, 99.2)
7 months	29	88.9 (5.3)	(78.6, 99.2)
8 months	27	88.9 (5.3)	(78.6, 99.2)
9 months	22	84.2 (6.7)	(71.0, 97.4)
10 months	20	84.2 (6.7)	(71.0, 97.4)
11 months	19	84.2 (6.7)	(71.0, 97.4)
12 months	11	84.2 (6.7)	(71.0, 97.4)
13 months	7	42.1 (30.0)	(0.0, 100.0)
14 months	7	42.1 (30.0)	(0.0, 100.0)
15 months	7	42.1 (30.0)	(0.0, 100.0)

CR = complete response, PDE = primary disease evaluation, PDE_{CR} = complete responders at the PDE visit.

^a N represents the estimated number of patients in each time point according to Kaplan-Meier estimates.

^b Nelson-Aalen estimate of SE was used for CIs.

Source: Study UT001 CSR Table 14.2.6.

The dichotomous analysis of CR at 12-month post-PDE Visit (Follow-up Visit 4/Study Completion Visit), based on the number of patients with observed response evaluation results (ie, excluding indeterminate results), is presented in Table 10. The table shows the number of patients who attended each follow-up visit and the number of patients who had a response evaluation at each visit. Of the 20 patients who reached Follow-up Visit 4 and had a response evaluation, 14 (70.0%) patients had durable CR at the 12-month post-PDE Visit (95% CI: 45.7, 88.2, p-value = 0.0129). The lower bound of the 95% CI was above 40%, indicating successful durability of response at the 12-month post-PDE Visit.

Table 15 Proportion of Patients With Durable CR at Follow-up Visits (PDE_{CR} Analysis Set)

Visit	Total N ^a	N ^b	n (%) of Patients ^c	95% CI (%)	p-value ^d
3-months post PDE/Follow-up 1	41	38	35 (92.1)	(78.6, 98.4)	0.0129
6-months post PDE/Follow-up 2	34	31	27 (87.1)	(70.1, 96.4)	
9-months post PDE/Follow-up 3	30	26	21 (80.8)	(60.6, 93.5)	
12-months post PDE/Follow-up 4 (Study Completion Visit)	25	20	14 (70.0)	(45.7, 88.2)	

Note: Durable CR results were carried backward. Only valid data were used, ie, “indeterminate” diagnosis was excluded. Indeterminate patients were those who had “Undetermined, were decided at the next visit” (or “not done”) on CRF form “Complete Response Durability Assessment” at follow-up visits and unscheduled visits, or had no unscheduled visits.

CR = complete response, CRF = case report form, PDE = primary disease evaluation, PDE_{CR} = complete responders at the PDE visit.

^a Number of patients who reached follow-up visit.

^b Number of patients who reached follow-up visit with response evaluation.

^c Percentage was calculated from the overall number of patients with response evaluation at each follow-up visit (N).

^d Exact binomial test versus pre-specified performance goal of 40%.

Source: Study UT001 CSR Table 14.2.8.

Subpopulation analyses were completed to assess the potential effects of demographic characteristics, baseline disease characteristics, and extent of treatment on the primary and key secondary endpoints. Overall, CR results were consistent across subgroups and no individual parameter demonstrated an impact on durability of response at 12-months post-PDE Visit

Other Efficacy Endpoints

The durability of tumor ablation effect of UGN-101 in patients who demonstrated CR at the PDE Visit was also evaluated at 3, 6, and 9 months following the PDE Visit as a secondary endpoint. Durability of response was estimated at a rate of 91.7% (95% CI: 82.8, 100.0), 88.9% (95% CI: 78.6, 99.2), and 84.2% (95% CI: 71.0, 97.4) at response evaluations 3-, 6-, and 9-months post-PDE Visit, respectively.

The dichotomous analysis of CR at the 3-, 6-, and 9-months post-PDE Visits was based on the number of patients with available response evaluation results (ie, excluding indeterminate results). Complete response was the observed response evaluation result for 35 (92.1%) out of 38 patients, 27 (87.1%) out of 31 patients, and 21 (80.8%) out of 26 patients at the 3-, 6-, and 9-months post-PDE Visits, respectively. The lower bound of the 95% CI was above 40% at each visit, indicating successful durability of response.

Target treatment area papillary lesion measurements were summarized by visit. At the PDE/Re-evaluation Visit, the mean number of lesions per patient was 1.3 (SD: ± 0.9) with a mean diameter of patients’ largest tumor of 9.3 mm (SD: ± 6.4), and a calculated total tumor

burden of 11.6 mm (SD: ± 11.5). Mean tumor diameter and mean tumor burden values were numerically higher at the PDE/Re-evaluation Visit than at Screening, likely due (at least in part) to the following:

- A subpopulation analysis of pre-debulking tumor burden demonstrated that more patients who were CR at the PDE Visit had a lower pre-debulking tumor burden (≤ 17 mm) than patients who were NCR at PDE Visit.
- Patients who were CR at PDE had no visible tumor burden by definition, thus characteristics were only included for patients who were NCR at the PDE/Re-evaluation Visit.

The Applicant's Position:

Results of other endpoints were in general supportive of the observed benefit at PDE and 12-months post PDE.

The FDA's Assessment:

The applicant submitted an efficacy update for durability of response based on a data cutoff (DCO) date of 18 December 2019. The median duration of response was not reached (range: 0, 18.8+ months). Seven patients who achieved CR experienced recurrence of disease at or prior to the 12 months post-PDE visit and 11 patients continue to be followed for duration of response without recurrence at the DCO date, including 9 who had either not yet reached the 12-month visit or were considered indeterminate for ongoing response at that visit.

FDA disagrees with the following aspects of presenting the key secondary endpoint:

1. Kaplan-Meier estimates of durability may be misleading if the follow-up data are immature. Since duration of CR is not mature, FDA computes the percentage of responding patients who remained in CR at the 12-month post-PDE visit without regards to censoring. Among the 41 patients who achieved a CR at PDE, 19 (46%) remained in CR at the 12 months post-PDE visit.
2. The presentation of the p-value for durable CR at the 12-month post-PDE Visit is not appropriate because this is a single arm trial and inferential procedures are not used.

FDA notes that patient (b) (6) was considered a CR, but had no subsequent follow-up data, and thus had a 0-month duration of response. Patient (b) (6) was read as "suspicious for high-grade disease" by both local and central pathology at the FU2 visit. The patient was determined to have recurrence at this time point.

8.1.2.11. Dose/Dose Response

The Applicant's Position:

Initially, patients with evaluation of response of CR at the PDE Visit were to undergo up to 11 additional once-monthly maintenance instillations of the same concentration in order to offer patients the best chance of maintaining a durable treatment response. However, investigators modified maintenance regimens based on a number of factors. Although patients were evaluated at each maintenance dose and discontinued if there was evidence of recurrent disease, there does not appear to be a relationship between the number of doses of maintenance received and the durability of response. These data indicate that patients are able to maintain a durable response to treatment without maintenance therapy, which may eliminate unnecessary additional repeated endoscopic manipulation and exposure to UGN 101.

The FDA's Assessment:

A relationship between dose of UGN101 and response to therapy cannot be determined due to the study design. The dose of UGN101 instilled into the pyelocalyceal system for each patient was based on individual measurements of the pyelocalyceal system. Ten patients did not complete the study treatment regimen of 6 weekly instillation of UGN101; nine of whom had response evaluated. Of these 9 patients, four patients (44%) achieved a CR by central pathology lab. Comparatively, of the 61 patients who completed all six treatment instillations, 60 patients were evaluated for response with 33 (55%) patient achieving CR.

8.1.2.12. Durability of Response

The Applicant's Position:

Durability of response was the key secondary endpoint. Results are described above.

The FDA's Assessment:

The median duration of response was not reached (range: 0, 18.8+ months). Among the 41 patients who achieved a CR at PDE, 19 (46%) remained in CR at the 12 months post-PDE visit. Refer to Section 8.1.2.10 for discussion of durability of response.

8.1.2.13. Persistence of Effect

Initially, a 12-month follow-up period was planned to assess durability of patients with CR at the PDE Visit. Per Agency request, long-term data on outcomes from patients who had completed the trial, both CR and NCR, were obtained where available.

The availability of the long-term follow-up data is summarized for all patients who had completed/terminated the study at the time of the interim CSR data cut (22 May 2019) (Table 11).

Table 16 Long Term Follow-up data Availability for Patients Who Completed or Terminated Study UT001

Status at PDE	Long Term Follow Up Data					No Long Term Follow Up Data			
	N ^a	n	Data Types		n	Reasons for No Long Term Follow Up Data			
			Upper and/or Lower Tract Carcinoma	CR Durability Assessment ^b		Died	Withdrew Consent	Insufficient Data ^c	Other ^d
CR	26	9	9	4	17	1	1	5	10
NCR	29	15	15	NA	14	2	1	11	0
Total	55	24	24	4	31	3	2	16	10

CR = complete response; FU = follow up; NA = not applicable; NCR = non-complete response; PDE = primary disease evaluation.

- a Patients who had completed/early terminated the study at the time of the interim CSR data cut (22 May 2019).
- b Reasons why patients who were CR did not provide long term CR durability data included: incorrect patient form provided (n = 1), recurrence at the 12-month FU visit (n = 1), or had cystoscopy but no ureteroscopy (n = 3).
- c Patients with insufficient data to be included in the long term FU analysis did not have data provided prior to the data cut date for this analysis, the data that was received required corrections and was not included, or the sites did not provide any data.
- d Patients had recently completed/terminated with in the 3 months prior to the data cut for the long term FU analysis. Thus the site was not contacted for additional information.

Source: Data on file.

UC After Study Completion or Termination

Bladder UC Occurrence: Data were provided for patients with CR (9 patients) and NCR (15 patients).

- Of the 9 patients with CR at the PDE Visit, 1 had no available information, 6 had no bladder UC after study completion, and 2 patients were diagnosed with bladder UC after study completion (both had bladder UC during the study as well).
- o Patient (b) (6) was a CR at PDE Visit on 05 Jul 2017. During the study, he was diagnosed with bladder UC on 10 Jul 2017, which was treated with lesion ablation and resolved on the same day. The patient's response was indeterminate at his 12-month post PDE visit during the study on 28 Jan 2019. The patient was diagnosed with bladder UC on 22 Apr 2019 (21 months and 18 days after the PDE Visit), but was a durable CR for UTUC on the same day.

- Patient (b) (6) was a CR at PDE Visit on 09 Jan 2018. During the study, he was diagnosed with bladder UC on 10 Apr 2018, which was treated with transurethral resection of bladder tumor (TURBT) and resolved on the same day. The patient was diagnosed with bladder UC again on 05 Jun 2018, which was treated with TURBT and resolved on 02 Oct 2018, and 26 Dec 2018, which was treated with TURBT and resolved the same day. The patient was durable for CR at his 12-month post PDE visit during the study on 27 Dec 2019. The patient was diagnosed with a recurrence of bladder UC on 01 Apr 2019 (14 months and 24 days after the PDE Visit) but was a durable CR for UTUC on the same day.
- Of the 15 patients with NCR at the PDE visit, 8 had no bladder cancer after study completion, and 7 patients were diagnosed with bladder UC after study completion (3 patients with PR and 4 patients with NR at the PDE Visit). Of the 8 patients with no bladder cancer after study completion, 4 patients had a history of bladder UC, and of the 7 patients with bladder cancer after the study, 3 had a history of bladder UC.

UTUC Recurrence or Progression: Data were provided for patients with CR (9 patients) and NCR (15 patients).

- Of the 9 patients with CR at the PDE Visit, 5 had no available information. Of the remaining 4 patients with CR at the PDE Visit, none had UTUC recurrence or progression to HG and or invasive disease after study completion.
- Of the 15 patients with NCR at the PDE Visit, 13 patients had UTUC diagnosed after study completion/termination.
- Three patients had progression of UTUC, of which 2 patients had progression with evidence of invasive disease.
- Two patients underwent RNU after study completion (1 with progression; 1 without).

CR Durability Assessment After Study Completion or Termination

There were 4 patients who were CR at the PDE Visit and had long term data for a CR durability assessment (out to 21 months post PDE). All of these patients demonstrated durable CR at the treated area.

The Applicant's Position:

Durability of response is a key secondary endpoint in Study UT001 which was designed to generate FU data on patients with a CR for up to 12 months. During presubmission discussions with the Agency, the level of follow up data at 6 months was discussed. Follow up data in this NDA include patients with up to 15 months from CR with 75% of patients with 6 months FU data. Durability of response was estimated at 84.2% (95% CI: 71.0, 97.4) at 12 months post CR by Kaplan-Meier analysis. The high CR rate coupled with the relatively low rate of recurrence in

this dataset support the clinical significance of the therapeutic outcome.

The FDA's Assessment:

There are limited data available to inform the long-term durability of responses seen with UGN-101. The FDA requested and the Applicant agreed to a post-marketing commitment to follow all patients in CR on UT101 for five years or until recurrence, progression, death, or loss to follow-up. The incidence of RNU will also be collected. However, note that determination of CR persistence will be made by the investigator and central pathology review is not planned.

Of the 71 patients treated on UT001, a total of 8 patients underwent RNU either during the study (2 patients) or during long-term follow-up subsequent to the 12-month follow-up visit (6 patients). The median time from first treatment to RNU was 191 days (range: 121, 403 days). Seven of these eight patients did not achieve a CR (or PR) at the PDE visit; one patient had achieved a CR.

Long-term follow-up data from the Compassionate Use Program (CUP):

Long-term follow-up data from the CUP were reviewed. This investigator-sponsored program was initiated in September 2014 and includes patients from the US, Europe, and Israel. A total of 18 patients with LG-UTUC enrolled in the CUP, of whom follow-up data was available for seven patients. Of these seven patients, seven experienced a CR and one discontinued after three treatments due to pancytopenia. Among the seven patients who achieved a CR, four recurred at 4, 9, 12, and 45 months after determination of CR, and one of these patients underwent RNU. The remaining two patients had no evidence of upper tract recurrence at 14 and 27 months. The patient who discontinued therapy prior to completion was reportedly without evidence of disease 45 months followed last administration. Overall these data provide limited supportive evidence of the duration of response seen with UGN-101 therapy given a potentially biased sample, limited data on baseline disease, no protocol-based assessment for disease, and no central pathology.

8.1.2.14. Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

Not Applicable

The FDA's Assessment:

No patient reported outcome data was submitted by the applicant for this NDA application.

8.1.2.15. Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

Not Applicable

The FDA's Assessment:

Not applicable.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

Clinical study UT001 was an open-label, single-arm clinical study of UGN-101 in 71 patients with LG-UTUC. The treatment regimen comprised of six instillations of UGN-101 administered weekly (Treatment Period), followed by 11 monthly instillations of UGN-101 (Maintenance Period). The primary endpoint is the rate of complete response at the Primary Disease Evaluation visit conducted 5 weeks after the last instillation of UGN101, i.e., at 3 months after treatment initiation. During FDA review, several issues with the conduct of the trial and analysis of the results were identified.

- Interpretation of urine cytology, which was a required component of the CR definition, was not adequately pre-specified. FDA evaluation of cytology results identified two patients with urine cytology results that precluded either CR at the PDE visit or durability of CR at a follow-up visit.
- Several patients had major protocol violations / deviations that could potentially have affected the outcome, predominantly related to missing central urine cytology results. While the primary endpoint of CR and secondary endpoint of durability of CR were based on local laboratory pathology results, central cytology/histopathology were used to corroborate the results. This was of added importance given the lack of pre-specification of cytology interpretation. However, there were no patients with suspicious local urine cytology for whom the central pathology result was missing, which reduces the potential impact of these missing results with regards to interpretation of the study outcome.
- There were geographic differences in the demographics and rate of CR between the top two enrolling sites (Sheba and MD Anderson). The Applicant noted that the baseline tumor burden differed between these two sites. The FDA considers this to be a plausible explanation. Additionally, the sample size for this subgroup was small and this difference may be due to chance.

The FDA calculated the CR rate to be 58% (95% CI: 45%, 69%), which is lower than the Applicant's reported CR rate of 59% (95% CI: 47%, 71%). The median duration of response was not yet reached and 19 patients remaining in CR at the 12-month visit. While the study had several uncertainties described above, there were no biases identified. These results are considered sufficiently clinically meaningful to overcome these uncertainties.

8.1.4. Assessment of Efficacy Across Trials

Data from studies to assess the efficacy of mitomycin gel for urinary bladder instillation (UGN-102) in patients with non-muscle invasive bladder cancer (NMIBC) provide further supportive evidence of the efficacy of the combination of mitomycin and hydrogel in UC. No additional efficacy data are considered other than the data described in Section 8.1.2.

Additional Efficacy Considerations

The FDA's Assessment:

The additional studies (BL001, BL002, BL003, and BL004) submitted in this application to support efficacy and safety are not applicable to this application. The investigation treatment is UGN-102 which has the same active cytotoxic agent, mitomycin, but different routes of administration (intravesical versus intrapylolocalyceal), as well as a different patient population (non-muscle invasive bladder cancer versus LG-UTUC). These differences do not allow an assessment of efficacy across trials.

8.1.5. Integrated Assessment of Effectiveness

The Applicant's Position:

In the pivotal Phase 3 study, instillation of UGN-101 once weekly for 6 weeks was the first demonstration of effective primary chemoablation of LG UTUC. A significant majority of patients were complete responders at the PDE visit. Although the study is ongoing, additional follow-up data indicate the persistence of durability up to and beyond the completion of the study out to 21 months post PDE, with few documented recurrences.

The FDA's Assessment:

The FDA considers the efficacy results of Study UT001, including a CR rate at 3 months of 58% (95% CI: 45%, 69%) with 19 (46%) patients remaining in CR at the 12-month visit to be clinically meaningful, despite the uncertainties and difficulties in interpretation noted above. While the study remains immature and the median duration of response has not been reached, the above results are considered sufficiently meaningful in the setting of the predominant alternative therapy being radical surgery to recommend regular rather than accelerated approval. The FDA requested and the Applicant agree to a PMC to continue to follow responding patients for response. The efficacy claims for UGN101 need to be balanced with the acknowledgement that this study is ongoing and 9 patients (five who had not reached the 12-month follow-up visit and four who were considered indeterminate for CR durability at the 12-month visit) continue to be

followed for response duration at the time of the review.

8.2. Review of Safety

The Applicant's Position:

This safety evaluation is primarily based on data from patients treated in the phase 3 trial UT001 and supported by the Phase 2 studies in NMIBC and a compassionate use program. The primary focus is on data from 71 patients treated with at least 1 dose of study drug in the prospective, open-label, single-arm, pivotal Phase 3 Study UT001 in patients with LG UTUC. Safety data has been provided for 3 Phase 2 clinical studies in 111 patients with NMIBC and are considered indirectly supportive in this application. In addition, exposure data from a Phase 1 study in 7 patients with muscle-invasive bladder cancer (MIBC), and safety narratives for a Compassionate Use Program in patients with LG UTUC were also included.

The justification for the single-arm approach in the pivotal Phase 3 Study was the absence of any non-surgical "ablative" therapy to which UGN-101 could be compared. In addition, UGN-101 was indicated as a nephron-sparing approach also for patients who were currently candidates for RNU, therefore, equivalent control and placebo arms were either not applicable or were not considered for ethical reasons.

Data from these studies allow for an informed assessment of the safety profile of UGN-101 and an evaluation of the overall benefit-risk in subjects with LG UTUC. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

Overall, this evaluation of the safety data provides support for the safety and tolerability of UGN-101 that is consistent with its intended use in the treatment of patients with LG UTUC.

The FDA's Assessment:

In addition to Study UT001, safety data from three Phase 2 studies were submitted to support the application, comprising 111 patients in total.

- BL002 (TC-BC-02) is an open-label dose-escalation clinical study of intravesical UGN-02 (mitomycin admixed with TC-3) administered in patients with non-muscle invasive bladder cancer (NMIBC). The Applicant submitted safety data for 18 patients enrolled in this study.
- BL003 (TAS-4M-CS-0002) is an open-label, randomized, active controlled clinical study of intravesical UGN-02 in patients NMIBC. The Applicant submitted safety data for 79 patients enrolled in this study.
- BL004 (TC-BC-10) is open-label, dose-escalation clinical study of UGN-02 in patients with NMIBC. The study was terminated early by the Sponsor after the first dosing cohort was enrolled. The Applicant submitted safety data for 14 patients enrolled in this study.

Comparison of these safety data from the three supportive clinical studies to UT001 is difficult as the study drug is different. While both drugs have the same active cytotoxic compound, mitomycin, UGN-101 is an admixture with TC-3 for pyelocalyceal injection and UGN-102 is an admixture with USP and UG-1 for intravesical injection. Additionally, the study population and tumor types are different tumor types: low-grade upper tract urothelial cancer versus non-muscle-invasive bladder cancer. Consequently, the applicability of safety data from these pooled studies is limited in the safety assessment for UGN-101 in LG-UTUC.

The FDA reviewed the 120-day safety datasets from Study UT001 submitted by the applicant and did not identify any new safety signals not already discussed in this review. Safety results presented in the review are as of the original data cut-off and do not reflect adverse event incidences from the 120-day safety update.

8.2.1. Safety Review Approach

The Applicant's Position:

The safety review presented in this NDA is a comprehensive analysis of safety data relevant to the use of UGN-101 in the treatment of patients with LG UTUC. Based on clinical experience and potential effects of mitomycin exposure, the following AESIs of UGN-101 were identified:

- AEs suggesting ureteral damage, urosepsis, urinary tract obstruction, and onset of renal insufficiency or deterioration of renal function following treatment initiation,
- AEs indicating bone marrow suppression,
- Allergic reactions to mitomycin (Common Terminology Criteria for AEs [CTCAE] Grade 3/4).

The FDA's Assessment:

The safety assessment for UT001 includes assessment of treatment-emergent adverse events, defined as AEs that started on or after the day of first instillation of UGN101. Adverse events were coded according to MedDRA dictionary version 19.1; and graded by the investigator according to CTCAE version 4.03. Adverse events of special interest (AESI) were identified to be:

1. Allergic reaction to mitomycin
2. Urosepsis
3. Ureteral events, including stenosis and symptoms suspicious of ureteral perforation/rupture (i.e., prolonged localized abdominal or flank pain, abdominal tenderness/acute abdomen)
4. Unexpected adverse drug reaction with severity grade of 3 or 4
5. 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. Bone marrow suppression
 - Anemia
 - Neutropenia
 - Leukopenia
 - Thrombocytopenia
 - Any change in myeloid cellularity which in the opinion of the local PI indicates of possible health risk to the patient.

FDA reviewed the incidence, duration, and outcome of procedures performed to treat an adverse event, particularly interventions required to address ureteral obstruction.

FDA reviewed patient narratives for patients who experienced death, SAE, AEs leading to discontinuation, and AESIs.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

The Safety evaluation included all subjects who received at least 1 dose of study treatment (Table 12). In Study UT001, exposure varied by patient because it was based on volumetric assessment performed at a given instillation and thus dependent on the anatomy of the collection system of the patient. Patients were exposed to mitomycin for a mean of 39.7 days in the treatment period and 154.1 days in the maintenance period. During the treatment period, patients received a total mean mitomycin dose of 217.5 mg (based on a mitomycin concentration of 4 mg/mL in the hydrogel) in a total UGN-101 mean volume of 54.4 mL across the 6 instillations. During the maintenance period, patients received a total mean mitomycin dose of 202.90 mg in a total mean volume of UGN-101 of 50.72 mL across the instillations in the maintenance period.

Table 17 Study Drug Exposure in Patients With LG UTUC (Study UT001)

Exposure	UGN-101 Volume (mL)	Mitomycin Dose (mg)	Number of Instillations
During the Treatment Period (N = 71)			
n receiving treatment		71	
Mean (SD)	54.4 (14.3)	217.5 (57.1)	5.8 (0.5)
Median (Min, Max)	54.0 (21.0, 90.0)	216.0 (84.0, 360.0)	6 (3, 6)
During the Maintenance Period (N = 41)			
n receiving treatment		29	
Mean (SD)	50.72 (35.49)	202.90 (141.94)	5.3 (3.0)
Median (Min, Max)	42 (7, 150)	168 (28, 600)	6 (1, 10)

CR = complete response, LG UTUC = low grade upper tract urothelial cancer; PDE = primary disease evaluation.
Source: Study UT001 Table 14.1.28, Table 14.1.30, and Table 14.1.33.

Study drug exposure in the pooled Phase 2 NMIBC studies was considered supportive of the assessment of safety in subjects who were representative of a related target population (Table 13). In the Phase 2 NMIBC studies, a total of 111 patients received at least 1 instillation (solution: 26 patients; gel: 85 patients). The majority of patients received 6 instillations (92.3% of the mitomycin solution group; 76.5% of the mitomycin gel group).

Table 18 Study Drug Exposure in Patients With NMIBC (Studies BL002, BL003, and BL004)

n (%)	Mitomycin				
	40 mg Gel N = 33	80 mg Gel N = 38	120 mg Gel N = 14	40 mg Solution N = 26	All Gel N = 85
At least 1 dose	33 (100.0)	38 (100.0)	14 (100.0)	26 (100.0)	85 (100.0)
1 dose	2 (6.1)	1 (2.6)	0 (0.0)	0 (0.0)	3 (3.5)
2 doses	1 (3.0)	0 (0.0)	2 (14.3)	0 (0.0)	3 (3.5)
3 doses	1 (3.0)	3 (7.9)	2 (14.3)	1 (3.8)	6 (7.1)
4 doses	3 (9.1)	1 (2.6)	2 (14.3)	0 (0.0)	6 (7.1)
5 doses	1 (3.0)	1 (2.6)	0 (0.0)	1 (3.8)	2 (2.4)
6 doses	25 (75.8)	32 (84.2)	8 (57.1)	24 (92.3)	65 (76.5)
1-2 dose(s)	3 (9.1)	1 (2.6)	2 (14.3)	0 (0.0)	6 (7.1)
3-4 doses	4 (12.1)	4 (10.5)	4 (28.6)	1 (3.8)	12 (14.1)
5-6 doses	26 (78.8)	33 (86.8)	8 (57.1)	25 (96.2)	67 (78.8)

NMIBC = non-muscle invasive bladder cancer.

Source: ISS Table 1.6.1.

In Study BL001, 7 patients were instilled once with either 40 mL of sterile hydrogel (n = 5) or 40 mg mitomycin mixed in 40 mL of sterile hydrogel (n = 2). The instillation was performed 6 hours prior to radical cystectomy. All patients underwent a macroscopic evaluation of their bladders immediately following excision to check for residual mitomycin sterile hydrogel. A

minimal amount of gel was observed in 2 patients. Thus, it is inferred that the gel dwell time was around 6 hours (which may also have been dependent on presurgical hydration).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The size of the safety database for UGN-101 in LG-UTUC is limited, but the duration of exposure was sufficient to evaluate the safety of UGN-101 in the indicated population. As previously noted, exposure to related compounds in different disease settings, including UGN-102 in NMIBC, was not considered strongly supportive for the proposed indication.

Incidence of adverse events was generally considered for the overall study duration rather than for the individual treatment and follow-up (maintenance) treatment periods, however safety for these two periods were described separately where it was deemed appropriate.

Relevant characteristics of the safety population:

The Applicant's Position:

The eligibility criteria in the pivotal Phase 3 Study UT001 were clinically relevant for the target population of subjects who would receive UGN-101 following regulatory approval in the proposed indication. In this study, the ITT and safety populations were identical. Please reference Section 8.1.2 for a description of the relevant characteristics of this population, including the substantial baseline morbidity in this older patient population (only 25.4% of patients were < 65 years old at Baseline).

This safety population was sufficiently diverse to represent the expected target population. The size and adequacy of the safety database are reflective of the rarity of the US target population.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Refer to FDA's assessment of Section 8.1.2 for additional details regarding the demographic characteristics of the patient population. The safety population was small and follow-up time was relatively short, though considered sufficient for the proposed indication. Low-frequency adverse events or those observed only with long-term follow-up may not have been observed during the conduct of Study UT001. Safety narratives from the compassionate use program provides additional limited long-term follow-up data.

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on data from the Phase 3 Study UT001 in 71 safety-evaluable patients with LG UTUC. This population allows for an informed assessment of the safety profile of the rare disease, LG UTUC and a judgment of the overall benefit-risk in subjects with exposure to the orphan drug, UGN-101. Notably, this 505(b)(2) application is also supported by the safety profile of the approved listed drug, mitomycin.

In addition, the safety profile is supported by data from the pooled Phase 2 Studies in 111 safety-evaluable patients with NMIBC and the 7 safety-evaluable patients from the Phase 1 study in MIBC; however, the toxicity to the target treatment organ (UUT) could not be assessed in these patient populations. Further details are provided above.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The Applicant also provided datasets for the three Phase 2 studies. These were not pooled with the data from Study UT001 by the Applicant or FDA for safety analysis due to differences in study population, study drug, and dose levels differences between the studies. The FDA agrees that the safety data from the three Phase 2 studies were generally consistent with the safety findings from the UT001 study and did not reveal any new safety signals. The 120-day safety data also did not reveal any new safety signals based on FDA review.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the CRFs and AE databases were consistent.

The FDA's Assessment:

Based upon the FDA's review and the findings of inspections by OSI, the FDA agrees with the Applicant's assessment regarding the quality and integrity of the submitted datasets. Refer to Section 4.1 in this document for further details on inspections.

Categorization of Adverse Event

The Applicant's Position:

The safety of study treatment in the target indication was evaluated on the basis of the:

- Frequency, severity, and causal relationship of AEs to study treatment and/or procedure.

- Frequency of deaths, SAEs, and other clinically significant AEs (including AEs leading to discontinuation and AEs requiring dose interruption and/or reduction).
- Frequency, severity, and causal relationship of AESIs (see Section 8.2.1) to study treatment and/or procedure.
- Frequency of AEs, SAEs, AESIs, and serious AESIs in key demographic subgroups (age, sex, body mass index [BMI], center), disease characteristics (renal function/baseline estimated GFR, number of kidneys tumor debulking at baseline, catheter size), and success on primary endpoint (CR at PDE).
- Changes in laboratory variables, with particular attention to Grade 3/4 abnormalities

In Study UT001, AEs and laboratory parameters were graded using CTCAE Version 4.03 (severity grades and allergic reaction grades), and AEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1. Verbatim terms were included in AE listings and were translated and categorized as PTs.

AEs were to be collected from the time a patient signed informed consent up to 30 days following the last administration of study drug unless the AE was suspected to be related to the study treatment, in which case the AE was to be reported regardless of timelines. AEs that started on or after the first day of study drug administration were considered to be treatment-emergent adverse events (TEAEs). Deaths due to any cause occurring during the trial period (including the FU period) were reported. Pregnancy was to be reported at any time during the trial and during 6 months following last instillation (if site became aware of the pregnancy).

Safety data from the pooled Phase 2 supportive studies also included analyses of AEs and deaths (AE terms were coded using MedDRA version 19.1).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The FDA's review used the following grouped terms to assess incidence of AEs.

- Ureteric Obstruction (GT)
 - o Ureteric stenosis
 - o Hydronephrosis
 - o Pelvi-ureteric obstruction
 - o Urinary tract obstruction
 - o Ureteric obstruction
 - o Obstructive uropathy
- Flank Pain (GT)
 - o Flank pain
 - o Back pain

- Urinary Tract Infection (GT)
 - Urinary tract infection
 - Pyelonephritis
 - Urinary tract infection fungal
- Hematuria (GT)
 - Hematuria
 - Hemorrhage urinary tract
- Renal Impairment (GT)
 - Renal impairment
 - Acute kidney injury
 - Renal failure
- Fatigue (GT)
 - Fatigue
 - Asthenia
- Abdominal Pain (GT)
 - Abdominal pain
 - Abdominal pain lower
- Bacteriuria (GT)
 - Asymptomatic bacteriuria
 - Bacteriuria
- Instillation Site Pain (GT)
 - Instillation site pain
 - Procedural pain

Routine Clinical Tests

The Applicant's Position:

All general blood and urine specimens were analyzed by the local laboratory. Laboratory assessments performed included complete blood count, liver and renal function tests, coagulation, urinalysis, and urine culture. Pregnancy urine tests were conducted in female participants of childbearing potential. At the specified visits, a full physical examination or urology-oriented physical examination was performed. The patient's physical condition was examined and documented. This included an examination of main body systems, with a focus on the urinary system. Vital signs (including heart rate and blood pressure, temperature, and respiration rate) were also taken. Subjects were questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by the subject during or between visits or through physical examination, laboratory test results, or other assessments.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.4. Safety Results

Deaths

The Applicant's Position:

Three deaths occurred during this program as of the data cutoff date for the CSR, all of which were treatment-emergent and occurred in Study UT001 (Table 14). All deaths occurred > 30 days after the last dose of study drug and were assessed as unrelated to study drug and study procedure.

Table 19 Deaths (Study UT001)

Exposure				Cause of Death Assessment			
Number of Instillations		Days From		Autopsy Performed	Associated PT	Cause	Description
TP	MP	First	Last				
Failure to thrive/Failure to thrive/Metabolism and nutrition disorders							
6	0	94	44	No	Failure to thrive	Failure to Thrive	Unknown
Death from suspected natural causes/Death/General disorders and administration site conditions							
6	0	142	107	Yes	None	Suspect natural causes	There was no overt cause of death such as myocardial infarction or pulmonary embolism. He could have suffered an arrhythmia. However, we cannot determine that by our examination
CVA/Cerebrovascular accident/Vascular disorders							
6	9	418	40	No	Cerebrovascular accident	Neurological	Cerebrovascular accident

Note: AEs of deaths are listed by Reported Term/PT/System Organ Class

AE= adverse event; MP = maintenance period; PT = preferred term; TP = treatment period.

Source: SCS Table 12 and SCS Table 13.

The FDA's Assessment:

The FDA's analysis of deaths in Study UT001 is generally consistent with that provided by the Applicant. All-cause death occurred in 4/71 (6%) of patients, of which three were considered TEAEs. The FDA reviewed all death narratives provided by the applicant. Although the death of Patient (b) (6) was reported as a TEAE, it occurred 107 days following the last administration of UGN-101 and was thus not reported in the USPI. Death in Patient (b) (6) is attributed by FDA reviewers to urinary tract infection despite the listed PT of 'failure to thrive' given the preceding events of vomiting, acute kidney injury, and positive urine culture. This is likely

consistent with instrumentation during UGN-101 instillation.

- Patient (b) (6) (Failure to Thrive). The patient is an 84 year-old white women with medical history of chronic kidney disease and bladder cancer (1998) with unknown prior treatment history. On D (b) (6), the patient experienced hydronephrosis G2 of the left kidney and ureter and recovered on D (b) (6). On D (b) (6), the patient experience acute kidney injury G1 and vomiting G3 for which she was hospitalized. Patient found to have elevated troponin and UTI. On D (b) (6), the patient experience SAE of failure to thrive and resulted in death. Autopsy was not performed.
- (b) (6) (unknown). The patient is an 86 year-old white women with a medical history of pacemaker. On D (b) (6), the patient experienced SAE of syncope G4 for which she was hospitalized. On D (b) (6), the patient was found on the floor and brought to hospital. CT of the head showed bilateral subdural collections. The hematoma was drain with burr hole drainage and the patient recovered on D (b) (6). On D (b) (6), the patient experienced a SAE of fall for which she was hospitalized. On D (b) (6), the family reported that “the patient died in his sleep at a skilled nursing facility”. Autopsy indicated that “the cause of death was suspected natural causes.”
- Patient (b) (6) (Stroke). The patient is 81 year-old white man with history of diabetes, coronary artery disease. On D (b) (6), the patient experienced hydronephrosis for which he was hospitalized. He was also found to have renal failure and UTI. On D (b) (6), the patient underwent diagnostic retrograde intrarenal surgery (RIRS) and a Double-J stent was inserted into the right upper urinary tract. On D (b) (6), renal failure and hydronephrosis resolved and patient was discharged. On D (b) (6), the patient experienced hydronephrosis and treated with balloon dilatation and ureteral stent insertion and recovered on D (b) (6). On D (b) (6), the patient experienced a loss of consciousness and fell. He was found to have CVA for which he was hospitalized. CT showed extensive brain hemorrhage and on D (b) (6), the patient died. An autopsy was not performed.

The 120-day safety updated identified an additional two patient deaths for which patient narrative are summarized below.

- Patient (b) (6) (metastatic urothelial carcinoma). The patient is an 83-year old Asian man with medical history of kidney ablation for UTUC. On D30, the patient experienced hypersensitivity reaction was given cetirizine and recovered on the same day. On D40, the patient developed thrombocytopenia and was given filgrastim and recovered on D46. Treatment was interrupted. On D (b) (6), the patient developed pancytopenia and was treated with filgrastim and platelet transfusion. Study treatment was discontinued and recovered on D (b) (6). On D (b) (6), the patient was diagnosed with metastatic urothelial carcinoma for which he was hospitalized. MRI of the chest showed para-aortic and aortocaval lymphadenopathy. CT guided biopsy of a retroperitoneal lymph node confirmed micro metastatic disease with both high grade and low grade UTUC. . Ureteroscopies and MRI did not show any evidence of disease in the L kidney. Urine cytology was normal. On D251 patient was treated with carboplatin and dose-reduced

gemcitabine. On D (b) (6), the patient experience generalized weakness, failure to thrive, decreased oral intake, and acute hypoxic respiratory failure for which he as hospitalized. On D (b) (6), the patient experienced respiratory arrest and died. Autopsy was not performed.

- Patient (b) (6). The patient is a 79 year-old white male with a medical history of HG-UTUC (2013), bladder transitional cell carcinoma Stage 0 (2013). Prior cancer treatment included mitomycin, BCG, nephrectomy, and kidney ablation. On D3, the patient experienced dermatitis allergic G2, eczema G2, and petechiae G2; was given cetirizine an diphenhydramine, triamcinolone; and recovered on D15. On D13, the patient experience renal dysfunction G1 and recovered on D20. ON D (b) (6), the patient experienced hydronephrosis and recovered on D (b) (6). On D (b) (6), the patient experienced ureteric obstruction for which the patient underwent balloon dilatation and ureteral stenting; and recovered don D (b) (6). On D (b) (6), the patient experienced fever and weakness for which he was hospitalized. The patient received IV fluids, vasopressors, and antibiotics. On D (b) (6), the patient experienced Acute Respiratory Failure, Septic Shock, Pneumonia, and Thrombocytopenia. On D (b) (6), the patient developed atrial fibrillation. On D (b) (6) the patient was transferred out of the ICU. On D (b) (6), the patient developed hypotension, blood cultures few Staphylococcus epidermidis and patient was treated with meropenem. On D (b) (6), the patient was transferred to rehab facility. On D (b) (6), the patient developed recurrent pneumonia and septic shock and was transferred to the ICU. On D (b) (6), the patient was discharged to skilled nursing facility. On D (b) (6), the patient died from events related septic shock, pneumonia, and hypotension.

Serious Adverse Events

The Applicant's Position:

A total of 26 (36.6%) patients in Study UT001 had treatment-emergent SAEs (Table 15). The maximum severity of the SAEs was reported as moderate (1 [1.4%] patient), severe (21 [29.6%] patients); life-threatening (1 [1.4%] patient), and fatal (3 [4.2%] patients).

SAEs reported in the treatment period for pooled Phase 2 studies in NMIBC are presented in Table 16. There was no clear trend in the most common SAEs for the mitomycin gel and mitomycin solution groups as the SAEs for each PT occurred in 1 patient in each group.

Table 20 Treatment-emergent SAEs (Study UT001 – Safety Analysis Set)

PT, n (%) ^a	N = 71
At least 1 SAE	26 (36.6)
Ureteric stenosis	5 (7.0)
Hydronephrosis	4 (5.6)
Flank pain	3 (4.2)

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PT, n (%) ^a	N = 71
Urosepsis	3 (4.2)
Chronic obstructive pulmonary disease	2 (2.8)
Dehydration	2 (2.8)
Dyspnoea	2 (2.8)
Haematuria	2 (2.8)
Urinary tract infection	2 (2.8)
Vomiting	2 (2.8)
Acute kidney injury	1 (1.4)
Acute respiratory failure	1 (1.4)
Arrhythmia	1 (1.4)
Asthenia	1 (1.4)
Cardiac failure acute	1 (1.4)
Cardiac failure chronic	1 (1.4)
Cardiac failure congestive	1 (1.4)
Cerebrovascular accident	1 (1.4)
Death	1 (1.4)
Failure to thrive	1 (1.4)
Fall	1 (1.4)
Groin pain	1 (1.4)
Hyperglycaemia	1 (1.4)
Hypersensitivity	1 (1.4)
Hyponatraemia	1 (1.4)
Iron deficiency anaemia	1 (1.4)
Pancytopenia	1 (1.4)
Pelvi-ureteric obstruction	1 (1.4)
Pericardial effusion	1 (1.4)
Pulmonary oedema	1 (1.4)
Pyelonephritis	1 (1.4)
Pyrexia	1 (1.4)
Subdural haematoma	1 (1.4)
Supraventricular tachycardia	1 (1.4)
Syncope	1 (1.4)
Ureteric obstruction	1 (1.4)
Urinary tract obstruction	1 (1.4)

Note: Patients with more than 1 episode of the same SAE are counted only once. PTs were coded using MedDRA version 19.1.

MedDRA = Medical Dictionary for Regulatory Activities; PT= preferred terms; SAE = serious adverse event.

Source: Study UT001 CSR Table 14.3.1.15.

Table 21 Treatment-emergent SAEs (Phase 2 NMIBC Studies – TP Safety Population)

SOC PT, n (%)	Mitomycin				
	40 mg Gel N = 33	80 mg Gel N = 38	120 mg Gel N = 14	40 mg SN N = 26	All Gel N = 85
At least 1 SAE	3 (9.1)	3 (7.9)	1 (7.1)	3 (11.5)	7 (8.2)
Asthenia	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Pain	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Penile oedema	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Urethral haemorrhage	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.2)
Hip fracture	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	1 (1.2)
Hypersensitivity	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	1 (1.2)
Lower urinary tract symptoms	0 (0.0)	1 (2.6)	0 (0.0)	0 (0.0)	1 (1.2)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (1.2)
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (1.2)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Facial bones fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)
Post procedural haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.8)	0 (0.0)

Note: Patients with more than 1 episode of the same SAE are counted only once. PTs were coded using MedDRA version 19.1. Only SAEs that occurred on or after the first dose of study drug up to PDE visit are summarized. AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; NMIBC = non-muscle invasive bladder cancer; PDE = Primary Disease Evaluation; PT = preferred term; SAE = serious AE, SN = solution; SOC = system organ class; TP = treatment period.
Source: ISS Table 2.8.1.1.

The FDA's Assessment:

The FDA generally agrees with the data presented above by the Applicant. The FDA reviewed SAEs using Grouped Terms (Table 20). Ureteric obstruction was the most common SAE and occurred in 11 (15%) patients, including 10 (14%) patients with Grade 3 ureteric obstruction. No Grade 4 or 5 ureteric obstruction were observed.

Table 22 Serious Adverse Events by Grouped Terms, Study UT001

SAE	Grades 1-4 n=71 (%)	Grade 3 n=71 (%)	Grade 4 n=71 (%)
Ureteric Obstruction (GT)	11 (15)	10 (14)	0 (0)
Ureteric stenosis	5 (7)	5 (7)	0 (0)
Hydronephrosis	4 (6)	3 (4.2)	0 (0)
Pelvi-ureteric obstruction	1 (1.4)	1 (1.4)	0 (0)
Ureteric obstruction	1 (1.4)	1 (1.4)	0 (0)
Urinary tract obstruction	1 (1.4)	1 (1.4)	0 (0)
Flank Pain (GT)	3 (4.2)	0 (0)	0 (0)
Flank pain	3 (4.2)	0 (0)	0 (0)
Urinary Tract Infection (GT)	3 (4.2)	3 (4.2)	0 (0)
Urinary tract infection	2 (2.8)	2 (2.8)	0 (0)
Pyelonephritis	1 (1.4)	1 (1.4)	0 (0)
Hematuria (GT)	2 (2.8)	2 (2.8)	0 (0)
Hematuria	2 (2.8)	2 (2.8)	0 (0)
Renal Dysfunction (GT)	1 (1.4)	1 (1.4)	0 (0)
Acute kidney injury	1 (1.4)	1 (1.4)	0 (0)
Fatigue (GT)	1 (1.4)	1 (1.4)	0 (0)
Asthenia	1 (1.4)	1 (1.4)	0 (0)
Source: adae.xpt			

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

In Study UT001, a total of 16 (22.5%) patients had TEAEs leading to study drug discontinuation during the treatment and maintenance periods. Of these, 13 (18.3%) patients discontinued due to TEAEs in the SOC of Renal and Urinary Disorders, and the most common TEAE leading to study drug discontinuation was Ureteric stenosis (6 [8.5%] patients) (Table 17). Other TEAEs leading to study drug discontinuation included Iron deficiency anaemia, Pancytopenia, Thrombocytopenia, and General physical health deterioration (Study UT001 CSR Table 14.3.1.12).

A total of 3 (4.2%) patients had AEs leading to study discontinuation: Death, Failure to thrive, and Cerebrovascular accident in 1 (1.4%) patient each (Study UT001 CSR Table 14.3.1.13). All 3 events that led to study discontinuation were fatal, occurred at least 30 days after the last dose of study drug, and were considered unrelated to study drug or study procedure.

Table 23 TEAEs in the Renal and Urinary Disorders SOC Leading to Treatment Discontinuation (Study UT001 – Safety Analysis Set)

PT, n (%)	N = 71
At least 1 event	13 (18.3)
Ureteric stenosis	6 (8.5)
Hydronephrosis	3 (4.2)
Urinary tract obstruction	3 (4.2)
Acute kidney injury	1 (1.4)
Haematuria	1 (1.4)
Obstructive uropathy	1 (1.4)
Renal failure	1 (1.4)
Renal impairment	1 (1.4)
Ureteric obstruction	1 (1.4)

Note: Patients with more than 1 episode of the same PT are counted only once. PTs were coded using MedDRA version 19.1.

MedDRA = Medical Dictionary for Regulatory Activities PT = preferred term; SOC = system organ class;

TEAE = treatment emergent adverse event.

Source: Study UT001 CSR Table 14.3.1.12.

The FDA's Assessment:

The FDA generally agrees with the data presented above by the Applicant. The FDA also reviewed adverse events leading to treatment discontinuation using Grouped Terms (Table 22). Renal dysfunction leading to treatment discontinuation occurred in 2 (2.8%) patients. No Grade 4 or 5 adverse events leading to treatment discontinuation were observed.

Table 24 Incidence of adverse events leading to treatment withdrawal by Group Term and Preferred Term, Study UT001

Grouped Term or Preferred Term	Grades 1-4 n=71 (%)	Grade 3 n=71 (%)
Ureteric Obstruction (GT)	13 (18)	2 (2.8)
Ureteric stenosis	6 (8)	1 (1.4)
Hydronephrosis	3 (4.2)	1 (1.4)
Urinary tract obstruction	2 (2.8)	0 (0)
Obstructive uropathy	1 (1.4)	0 (0)
Ureteric obstruction	1 (1.4)	0 (0)
Renal Dysfunction (GT)	2 (2.8)	0 (0)
Renal failure	1 (1.4)	0 (0)
Renal impairment	1 (1.4)	0 (0)
Source: adae.xpt		

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

The mean time from the day of first treatment to the start of the first TEAE that led to temporary treatment interruption was 25.6 days and the time to treatment discontinuation was 41.1 days. The mean time from the day of first treatment to the start of the first treatment-emergent SAE that led to temporary treatment interruption was 18.7 days and the time to treatment discontinuation was 41.5 days.

The FDA's Assessment:

The FDA generally agrees with the data presented above by the Applicant. The FDA reviewed of adverse events leading to treatment Interruption and dose reduction using Grouped Terms (Table 23). Renal dysfunction GT leading to treatment interruption occurred in 8 (11%) patients. Ureteric Obstruction GT leading to treatment interruption occurred in 8 (11%) patients. There were few adverse events leading to dose reduction. One occurrence of Back pain Grade 2 and Groin pain Grade 2 leading to dose reduction were observed (Table 24). No Grade 4 or 5 adverse events leading to treatment interruption or dose reduction were observed.

One additional patient experienced Grade 1 ureteric obstruction leading to discontinuation as of the 120-day safety update.

Table 25 Incidence of adverse events leading to treatment interruption by Group Term and Preferred Term, Study UT001

Grouped Term or Preferred Term	Grades 1-4 n=71 (%)	Grade 3 n=71 (%)
Renal Dysfunction (GT)	8 (11)	1 (1.4)
Renal impairment	7 (10)	0 (0)
Acute kidney injury	2 (2.8)	0 (0)
Renal failure	1 (1.4)	1 (1.4)
Ureteric Obstruction (GT)	7 (10)	2 (2.8)
Urinary tract obstruction	3 (4.2)	1 (1.4)
Hydronephrosis	2 (2.8)	0 (0)
Ureteric stenosis	2 (2.8)	1 (1.4)
Urinary Tract Infection (GT)	6 (8)	1 (1.4)
Urinary tract infection	5 (7)	0 (0)
Pyelonephritis	1 (1.4)	1 (1.4)
Flank Pain (GT)	3 (4.2)	1 (1.4)
Flank pain	3 (4.2)	1 (1.4)
Abdominal Pain (GT)	2 (2.8)	0 (0)
Abdominal pain	1 (1.4)	0 (0)
Abdominal pain lower	1 (1.4)	0 (0)
Hematuria (GT)	1 (1.4)	0 (0)
Hematuria	1 (1.4)	0 (0)
Source: adae.xpt		

Table 26 Incidence of adverse events leading to dose reduction by Group Term and Preferred Term, Study UT001

Grouped Term or Preferred Term	Grades 1-4 n=71 (%)	Grade 3 n=71 (%)
Flank Pain (GT)	1 (1.4)	0 (0)
Back pain	1 (1.4)	0 (0)
Source: adae.xpt		

Significant Adverse Events

The Applicant's Position:

Overall, 54 (76.1%) patients experienced AESIs, with 46 (64.8%) patients having AESIs considered study drug - or procedure-related (Table 18). A total of 16 (22.5%) patients

experienced serious AESIs; 14 (19.7%) patients experienced study drug - or procedure-related serious AESIs and 1 (1.4%) patient experienced an AESI of Pyelonephritis that was assessed as a suspected unexpected serious adverse reaction (SUSAR). No patient experienced a serious AESI that led to death. A total of 14 (19.7%) patients discontinued treatment due to an AESI, of which 13 (18.3%) patients had AESIs that were considered by the investigator to be study drug - or procedure-related.

Table 27 Summary of Treatment-emergent AESIs (Study UT001 - Safety Analysis Set)

Patients With at Least 1, n (%)	N = 71
AESI	54 (76.1)
Serious AESI	16 (22.5)
AESI leading to death	0 (0.0)
Unexpected and related serious AESI (SUSAR)	1 (1.4)
AESI leading to treatment discontinuation	14 (19.7)
Study drug- or procedure-related AESI	46 (64.8)
Study drug- or procedure-related, serious AESI	14 (19.7)
Study drug- or procedure-related AESI leading to treatment discontinuation	13 (18.3)
Study drug-related AESI	42 (59.2)
Study drug-related, serious AESI (serious adverse reaction)	12 (16.9)
Procedure-related AESI	32 (45.1)
Procedure-related serious AESI	11 (15.5)

AESI = Adverse Events of Special Interest; SUSAR = suspected unexpected serious adverse reaction.

Note: Study drug- or procedure-related AESIs are defined as any AESI possibly, probably, or definitely related.

Source: Study UT001 CSR Table 14.3.1.23.

Renal and Urinary Disorders SOC:

- Summary:** 48 (67.6%) patients had treatment-emergent AESIs from the Renal and urinary disorders SOC that were both predefined and identified by manual review of all AEs in the renal urinary SOC, of which 14 (19.7%) patients had serious AESIs, and 1 (1.4%) patient had an SAE of Pyelonephritis that was a SUSAR (PT: Pyelonephritis). No AESIs from the Renal and urinary disorders SOC led to death. A total of 12 (16.9%) patients discontinued treatment due to an AESI from the Renal and urinary disorders SOC; however, none withdrew from the study.
- Severity:** Reported as mild in 18 (25.4%) patients, moderate in 15 (21.1%) patients, severe in 14 (19.7%) patients, and life threatening in 1 (1.4%) patient; none were fatal.
- Outcome:** The most commonly reported AESIs from the Renal and urinary disorders SOC (≥ 5 patients) included Ureteric stenosis in 31 (43.7%) patients, Renal impairment in 14 (19.7%) patients, Hydronephrosis in 13 (18.3%) patients, and Acute kidney injury in 5 (7.0%) patients. Overall, 24 (33.8%) patients had at least 1 AESI that was ongoing, 3 (4.2%)

patients had AESIs that resolved with sequelae, and 21 (29.6%) patients had AESIs that resolved at the time of last evaluation (Table 19). Of AESIs from the Renal and urinary disorders SOC that occurred in ≥ 5 patients, 13 of 31 patients with TEAEs of Ureteric stenosis, 9 of 14 patients with TEAEs of Renal impairment, 12 of 13 patients with TEAEs of Hydronephrosis and 3 of 5 patients with TEAEs of Acute kidney injury recovered from these respective AESIs.

4. **Seriousness:** A total of 14 (19.7%) patients experienced AESIs in the Renal and urinary disorders SOC that were classified as SAEs: ureteric stenosis, 5 (7.0%) patients; hydronephrosis, 4 (5.6%) patients; urosepsis, 3 (4.2%) patients; acute kidney injury, 1 (1.4%) patients; pelvi-ureteric obstruction, 1 (1.4%) patients; pyelonephritis, 1 (1.4%) patients; ureteric obstruction, 1 (1.4%) patients; urinary tract obstruction, 1 (1.4%) patients.
5. **Upper tract narrowing:** Patients with AESIs suggesting ureteral damage had additional data collected describing their events (n = 41). Of these, 18 (43.9%) experienced pain, 12 (29.3%) patients had compromised urine output associated with the event, 22 (53.7%) patients had associated hydronephrosis, and 13 (18.3%) patients reported a TEAE of hydronephrosis. A total of 38 (92.7%) patients experienced upper tract narrowing that required intervention, such as insertion of a stent in 34 (82.9%) patients, or balloon dilation in 15 (36.6%) patients. Two patients with an SAE of Ureteric stenosis elected to have nephroureterectomy (SCS Section 4.2.2)

Table 28 Treatment-emergent AESIs in the Renal and Urinary Disorders SOC by Worst Outcome (Study UT001 – Safety Analysis Set)

PT, n (%)	N = 71			
	Recovered	Recovered with Sequelae	Not Recovered	Total
At least 1 AESI	21 (29.6)	3 (4.2)	24 (33.8)	48 (67.6)
Ureteric stenosis	13 (18.3)	2 (2.8)	16 (22.5)	31 (43.7)
Renal impairment	9 (12.7)	0 (0.0)	5 (7.0)	14 (19.7)
Hydronephrosis	12 (16.9)	0 (0.0)	1 (1.4)	13 (18.3)
Acute kidney injury	3 (4.2)	1 (1.4)	1 (1.4)	5 (7.0)
Pelvi-ureteric obstruction	2 (2.8)	0 (0.0)	2 (2.8)	4 (5.6)
Renal failure	2 (2.8)	0 (0.0)	2 (2.8)	4 (5.6)
Urinary tract inflammation	1 (1.4)	0 (0.0)	3 (4.2)	4 (5.6)
Urinary tract obstruction	3 (4.2)	0 (0.0)	1 (1.4)	4 (5.6)
Urosepsis	3 (4.2)	0 (0.0)	0 (0.0)	3 (4.2)
Ureteric obstruction	1 (1.4)	1 (1.4)	0 (0.0)	2 (2.8)
Urinary retention	1 (1.4)	0 (0.0)	1 (1.4)	2 (2.8)
Kidney fibrosis	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.4)
Obstructive uropathy	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
Pyelonephritis	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.4)
Tubulointerstitial nephritis	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
Ureteral polyp	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.4)

PT, n (%)	N = 71			
	Recovered	Recovered with Sequelae	Not Recovered	Total
Ureteral spasm	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.4)
Ureteric injury	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.4)
Urethral stenosis	1 (1.4)	0 (0.0)	0 (0.0)	1 (1.4)

Note: Patients with more than 1 episode of the same PT are counted only once. PTs were coded using MedDRA version 19.1.

AESI = Adverse Event of Special Interest; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = System Organ Class.

Source: Study UT001 CSR Table 14.3.1.32.

Allergic Reaction to Mitomycin

6. **Summary:** The incidence of these events was Dermatitis allergic, 2 (2.8%) patients, and Hypersensitivity, 2 (2.8%) patients.
7. **Severity:** Allergic reactions to mitomycin were mild, 1 (1.4%) patient; moderate, 2 (2.8%) patients; or severe, 1 (1.4%) patient.
8. **Seriousness:** One patient had a TEAE of Hypersensitivity that was Grade 3 (severe) SAE. This event occurred on the day of Treatment 4 and was associated with the administration of tamsulosin for infection prophylaxis.

Other AEs potentially suggestive of allergic reaction (> 5%) included Pruritus in 9 (12.7%) patients and Rash/Rash generalized in 6 (8.5%) patients. These events were Grade 1 and 2 in nature and were not assessed as AESIs.

Blood and Lymphatic System Disorders SOC:

Overall, 15 (21.1%) patients experienced treatment-emergent AESIs from the Blood and lymphatic system disorders SOC. These AESIs were mostly mild in 10 (14.1%) patients, and all but 1 were non-serious.

9. **Anemia:** 9 (12.7%) patients with TEAEs that were of mild or moderate maximal severity. No patient had a TEAE of Anemia classified as an SAE. These were likely due to multiple etiologies in this patient population.
10. **Leukopenia:** 4 (5.6%) patients with TEAEs, all of mild maximum severity. No patient had a TEAE of Leukopenia classified as an SAE. In patients with normal white blood cell counts at baseline, the worst shift was to Grade 2 in 2 patients. In addition, 1 patient each shifted from Grade 1 at baseline to Grade 2 during the study and from Grade 2 at baseline to Grade 3 during the study. All 4 patients with leukopenia recovered during the study and no patients terminated from treatment due to this AESI.
11. **Pancytopenia:** 3 (4.2%) patients with TEAEs that were of mild (2 [2.8%] patients) or severe (1 [1.4%] patient) maximal severity. One (1.4%) patient had TEAE of Pancytopenia that was

classified as an SAE. All 3 patients with pancytopenia recovered during the study and no patients terminated from treatment due to this AEsI.

12. **Thrombocytopenia:** 3 (4.2%) patients with TEAEs of mild (1 [1.4%] patient) or severe (2 [2.8%] patients) maximal severity. No patient had a TEAE of Thrombocytopenia classified as an SAE. During the study, the worst shifts were to Grade 3 in 1 patient with normal platelet counts at baseline and in 1 patient with a Grade 1 decrease at baseline. All 3 patients with thrombocytopenia recovered during the study, and 1 patient terminated from treatment due to this AEsI.
13. **Leukocytosis:** 1 (1.4%) patient with a TEAE of mild maximal severity. No patient had a TEAE of Leukocytosis classified as an SAE. The patient recovered during the study and did not terminate treatment due to this AEsI.

The FDA's Assessment:

Allergic Reaction / Hypersensitivity:

Dermatitis allergic in 2.8% of patients and Hypersensitivity in 2.8% of patients were identified as preferred terms related to possible allergic reaction. One patient experienced a Grade 3 Hypersensitivity ((b) (6)) following his fourth treatment. No hypersensitivity reactions lead to treatment withdrawal, interruption, or reduction.

FDA reviewed adverse events considered possibly related to allergic reactions.

1. Hypotension, dizziness, and syncope occurred in five patients (7%) including a Grade 3 hypotension ((b) (6)) and Grade 3 syncope ((b) (6)). Neither of these Grade 3 events was considered clearly related to an allergic or hypersensitivity reaction.
2. Skin and subcutaneous tissue disorders (SOC) were observed in 17 patients (24%). Three adverse events were observed in more than one patient: Pruritus, Rash, Rash generalized. There were no Grade 3, 4, or 5 adverse events. One patient ((b) (6)) experienced Grade 2 urticaria that lead to interruption of the treatment and recovered from this AE.

Rare cases of allergic dermatitis due to intravesical mitomycin C have been reported, however the FDA considered that there was insufficient evidence of severe hypersensitivity to UGN-101 to require inclusion in Section 5: Warnings and Precautions or as a contraindication.

Renal Dysfunction:

Renal Dysfunction (Grouped Term), includes Renal impairment Acute kidney injury, and Renal failure; and was observed in 18 patients, including Grade 3 renal dysfunction in two patients (2.8%). No Grade 4 or 5 events were observed. Renal dysfunction did not resolve or resolved with sequelae in 50% (9/18) of these patients. Of these patients, the treatment was withdrawn in two patients; and treatment was interrupted in eight patients.

Of note, no Grade 3 or 4 laboratory incidences of creatinine increased occurred in UT001, there was a 10% incidence of Grade 3 chronic kidney disease, which refers to eGFR or CrCl that has decreased to 15-29 ml/min/1.73 m². This highlights the frail and elderly population enrolled on UT001 as relatively small absolute changes in creatinine may have resulted in marked decreases in renal function. As noted above, ureteric obstruction was associated with increased serum creatinine in 7 patients.

120-day Safety Update

The update identified one additional patient who experienced hydronephrosis that required ureteral stenting. No other changes were made to this analysis.

Ureteral Obstruction and Bone Marrow Toxicity: See discussion in Section 8.2.5.

Treatment-emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Most Frequent AEs

In Study UT001, the most commonly reported SOC for TEAEs included Renal and urinary disorders (59 [83.1%] patients), Gastrointestinal disorders (31 [43.7%] patients), and General disorders and administration site conditions (28 [39.4%] patients). The most frequently reported TEAEs were Ureteric stenosis (31 [43.7%] patients), Urinary tract infection (23 [32.4%] patients), Hematuria (22 [31.0%] patients), and Flank pain (21 [29.6%] patients)

In the Phase 2 NMIBC studies, the most common PT overall was dysuria (38.5% of the mitomycin solution group; 58.8% of the mitomycin gel group). The second most common PT for AEs was Urinary tract infection in the mitomycin solution (11.5%) and Hematuria in the mitomycin gel group (18.8%).

Adverse Drug Reactions

Table 20 summarizes the TEAEs reported in ≥ 10% (any grade) and the Grade 3 and 4 TEAEs reported in ≥ 5% of patients by SOC and PT.

Most adverse drug reactions in association with UGN-101 were predominantly Grade 1 or Grade 2 in intensity, and the majority of these events are consistent with the indication and/or administration of the study drug directly into the target organ. Grade 3 or 4 adverse reactions were infrequent, with the exception of Ureteric stenosis (6 [8.5%] patients) and Hydronephrosis (4 [5.6%] patients).

Table 29 TEAEs Reported in $\geq 10\%$ (Any Grade) or $\geq 5\%$ (Grade 3/4) of Patients (Study UT001 - Safety Analysis Set)

SOC PT, n (%)	N = 71	
	Maximum Severity Grade	
	All Grades	Grade 3 or 4
Number of patients reporting at least 1 TEAE	67 (94.4)	30 (42.3)
Renal and urinary disorders	59 (83.1)	18 (25.4)
Ureteric stenosis	31 (43.7)	6 (8.5)
Urinary tract infection	23 (32.4)	2 (2.8)
Haematuria	22 (31.0)	2 (2.8)
Flank pain	20 (28.2)	2 (2.8)
Dysuria	15 (21.1)	0 (0.0)
Renal impairment	14 (19.7)	1 (1.4)
Hydronephrosis	13 (18.3)	4 (5.6)
Pollakiuria	9 (12.7)	0 (0.0)
Gastrointestinal disorders	31 (43.7)	4 (5.6)
Nausea	17 (23.9)	1 (1.4)
Vomiting	14 (19.7)	3 (4.2)
Abdominal pain	13 (18.3)	1 (1.4)
General disorders and administration site conditions	28 (39.4)	1 (1.4)
Fatigue	11 (15.5)	0 (0.0)
Asthenia	8 (11.3)	1 (1.4)
Chills	8 (11.3)	0 (0.0)
Pyrexia	8 (11.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	19 (26.8)	1 (1.4)
Back pain	9 (12.7)	0 (0.0)
Blood and lymphatic system disorders	17 (23.9)	3 (4.2)
Anaemia	9 (12.7)	0 (0.0)
Skin and subcutaneous tissue disorders	17 (23.9)	0 (0.0)
Pruritus	9 (12.7)	0 (0.0)

Note: Patients with more than one episode of the same SOC or PT are counted only once. PTs were coded using MedDRA version 19.1. Severity grades are defined as 1 = mild, 2 = moderate, 3 = severe, 4 = life threatening, 5 = fatal.

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class;

TEAE = treatment-emergent adverse event.

Source: ISS Table 14.3.1.41.

The FDA's Assessment:

FDA reviewed adverse events that were considered not to be Treatment Emergent by the Applicant. Eleven patients experienced 31 non-treatment emergent adverse events (Table 28), including one grade 3 adverse event of Acute kidney injury and ureteric obstruction. No grade 4 or 5 non-treatment emergent adverse events were reported. Overall, the analysis did not

reveal any additional significant safety findings.

Table 30 Non-treatment emergent adverse events, Study UT001

Preferred Term	Grades 1-4 n=71 (%)	Grade 3 n=71 (%)
Asymptomatic bacteriuria	3 (4.2)	0 (0)
Acute kidney injury	1 (1.4)	1 (1.4)
Constipation	1 (1.4)	0 (0)
Flank pain	1 (1.4)	0 (0)
Gout	1 (1.4)	0 (0)
Hematuria	1 (1.4)	0 (0)
Lip swelling	1 (1.4)	0 (0)
Lower urinary tract symptoms	1 (1.4)	0 (0)
Micturition urgency	1 (1.4)	0 (0)
Perineal rash	1 (1.4)	0 (0)
Pollakiuria	1 (1.4)	0 (0)
Renal impairment	1 (1.4)	0 (0)
Stomatitis	1 (1.4)	0 (0)
Tooth infection	1 (1.4)	0 (0)
Ureteric obstruction	1 (1.4)	1 (1.4)
Urinary tract infection	1 (1.4)	0 (0)
Vaginal inflammation	1 (1.4)	0 (0)
Source: adae.xpt		

Laboratory Findings

The Applicant's Position:

Hematology

The majority of test results remained within the classification at Baseline with the majority of patients having a Grade 0 at baseline and remaining there or worsened by 1 Grade at the worst post Baseline grade assessment. There were few patients ($n \leq 2$) who worsened more than 1 Grade level in hematological parameters, with the exceptions of Neutrophil count decreased ($n = 3$) and Lymphocyte count decreased ($n = 7$). The only parameters with post Baseline worsening to Grade 3 assessment and with $n > 1$ patients were Lymphocyte count decreased ($n = 2$), Platelet count decreased ($n = 2$). There were no Grade 4 assessments (see Summary of Clinical Safety (SCS) Section 3.2.1 for additional information).

Of note, the hematological parameter with the most substantial shift was a worsening in Grade shift in anemia in 23 (32.4%) patients (eg, 19 [26.8%] patients from Grade 0 to Grade 1 or 2 and 4 [5.6%] patients from Grade 1 to Grade 2).

Renal Function

The majority of test results remained within the classification at baseline with the majority of patients having a Grade 0 at baseline and remaining there or worsened by 1 Grade at the worst post-Baseline grade assessment. There were few patients ($n \leq 2$) who worsened more than 1 Grade level in renal function test parameters with the exceptions of Creatinine increased ($n = 5$), Hyperuricemia ($n = 9$), Hyperkalemia ($n = 3$) and Hypoalbuminemia ($n = 5$). The only parameters with post baseline worsening to Grade 3 assessment and with $n > 1$ patients were CKD ($n = 3$) and Hyperuricemia ($n = 9$). There were no Grade 4 assessments (see SCS Section 3.2.2 for additional information).

Liver Function and Other Laboratory Analyses

The majority of liver function tests results remained within the classification that the patients had at Baseline, and there were no clinically relevant findings related to liver function, coagulation, urinalysis or urine dipstick test results. No results were indicative of drug-induced liver injury (DILI).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Refer to discussion of adverse events of special interest above for further analysis regarding renal function and hematology laboratory findings.

Vital Signs

The Applicant's Position:

During Study UT001, most patients (64 [90.1%]) had a potentially clinically significant vital sign values; however, most appeared to be due to transient increases or decreases in systolic blood pressure (change from baseline of ± 20 points), diastolic blood pressure (change from baseline of ± 15 points), or pulse rate (change from baseline of ± 15 points). There were few patients during the study with systolic blood pressure ≥ 180 mmHg, 4/71 (5.6%), or < 90 mmHg, 1/71 (1.4%); diastolic blood pressure ≥ 105 mmHg, 1/71 (1.4%), or ≤ 50 mmHg, 3/71 (4.2%); or pulse rate ≥ 120 , none, or ≤ 50 bpm, 7/71 (9.9%).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Electrocardiograms (ECGs)

The Applicant's Position:

ECG monitoring is not required in the Prescribing Information for the RLD and was not considered for Study UT001 given the local administration of mitomycin and subsequent limited systemic absorption. In addition, ECGs were assessed twice in the general toxicology study (first and last week of dosing) and no effect of the retrograde instillation with mitomycin gel was observed on qualitative or quantitative ECG parameters (Section 5.5.1).

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

QT

The Applicant's Position:

Not Applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that QT was not assessed in the submission. Additionally, systemic exposure to mitomycin via UGN-101 administration is expected to be minimal.

Immunogenicity

The Applicant's Position:

Not Applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

8.2.5.1. Risks to the Renal and Urinary Tract

Renal and Urinary tract AEs were expected based on clinical experience. Although it is less invasive than the current standard of care for LG UTUC, therapy with UGN-101 is not without risk. These included the effects of chemotherapy on the target organ, effects due to the route

of administration (potential procedural risks associated with insertion of an endoscope and ureteral catheter, which require urethral manipulation and X-ray-guided UUT manipulation), and effects due to the presence of the disease. Thus AESIs suggesting ureteral damage, urinary tract obstruction, onset of renal insufficiency or deterioration of renal function, and urosepsis were determined from the SOC of Renal and urinary disorders.

Overall, of the 71 patients who received at least 1 instillation of the study drug, 67 (94.4%) patients experienced TEAEs, the majority of which were considered related to the study drug or procedure. The majority of the observed TEAEs from this study were classified as part of the Renal and urinary disorders SOC as expected, as were the most frequently reported TEAEs in this study (> 25% of patients) of Ureteric stenosis, Urinary tract infection, Hematuria, and Flank pain. Just over a third of the patients experienced treatment-emergent SAEs, with the majority assessed as related to the study drug or procedure and the highest frequency of these SAEs occurring in the Renal and urinary disorders SOC.

The majority of patients had treatment-emergent AESIs in the Renal and urinary disorders SOC (48 [67.6%] patients), most of which were considered related to the study drug or procedure (43 [60.6%] patients). The most commonly reported AESIs from the Renal and urinary disorders SOC (≥ 5 patients) included Ureteric stenosis, Renal impairment, Hydronephrosis, and Acute kidney injury. A total of 14 (19.7%) patients experienced serious AESIs in the Renal and urinary disorders SOC. As of the data cut-off date, 42% of patients with reported AESIs of Ureteric stenosis, and the majority of patients with AESIs of Renal impairment, Hydronephrosis and Acute kidney injury had recovered from these events. Of the AESIs that occurred in ≥ 5 patients: 13 of 31 patients with reported Ureteric stenosis, 9 of 14 patients with Renal impairment, 12 of 13 patients with Hydronephrosis, and 3 of 5 patients with Acute kidney injury recovered from these events. Of note, a higher proportion of patients with CR by PDE (36 [85.7%] patients) experienced AESIs in the Renal urinary disorders SOC by PDE compared to the proportion of patient who did not achieve CR at PDE (12 [41.4%] patients).

Ureteral stenosis is a known and expected complication of endoscopic surgical management of upper tract tumors. The contemporary literature documents that up to 51% of patients undergoing ablative therapy for the treatment of LG UTUC experience ureteral stenosis. In this study, patients experienced renal pelvic and ureteral edema (contributing to ureteral stenosis); 41.9% (13 of 31) of patients with Ureteric stenosis TEAEs had recovered as of the data cutoff date. Whether these events should be attributed to repeated endoscopic manipulation, exposure to UGN-101 or both remains unresolved; however, the data from this trial suggest that ureteral stenosis that is associated with permanent scar formation that requires additional surgical intervention and compromises renal function was uncommon, that the rate of ureteral stenosis with instillation of UGN-101 was consistent with the rate associated with other forms of therapy for the conservative management of LG UTUC, and that the risk was preferable to RNU from a clinical perspective. Of note, transient ureteral inflammation and edema were relatively common in this trial, an expected outcome of mitomycin exposure and study

procedure, and is reflected by the majority of TEAEs of Ureteric stenosis being mild or moderate in severity.

The risk of infection due to the instillation procedure was manageable. Most patients received antimicrobial prophylaxis per American Urological Association guidelines, and while a significant proportion of patients had UTIs, more serious events such as urosepsis and pyelonephritis were seen infrequently.

Renal insufficiency or deterioration of renal function following treatment initiation were reported as TEAEs of Renal impairment, Acute kidney injury, or Renal failure. The majority of these TEAEs were not severe, only 1 of these was an SAE (PT: Acute kidney injury). Based on clinical laboratory assessments, the majority of test results remained within the severity classification at Baseline with the majority of patients having a Grade 0 at baseline and remaining there or decreased by 1 Grade at the worst post baseline grade assessment. The only parameters with post baseline worsening to Grade 3 assessment and with $n > 1$ patients were Chronic kidney disease ($n = 3$) and Hyperuricemia ($n = 9$).

1. Three patients had shifts from Grade 2 at Baseline (range: 39.38 to 42.12 mL/min/1.73 m²) to Grade 3 during treatment for eGFR values (range: 19.89 to 27.85 mL/min/1.73 m²). Two of these patients still had Grade 3 values at the last evaluation, while the other patient had an improvement back to Grade 2 at the last evaluation.
2. See SCS Section 3.2.2 for additional information including the change in uric acid values for the 9 patients with Hyperuricemia.

There were no Grade 4 assessments.

Most AESIs in the Renal and urinary disorders SOC were mild to moderate in severity. The toxicity within the UUT was considered consistent with the disease under study and the mode of administration of UGN-101.

The current standard of care requires continuous monitoring for organ-sparing therapy. In addition to monitoring, the following risk minimization measures will also be implemented:

14. Risks of AEs in the renal and urinary tracts are covered in the labeling in Section 5 (Warnings and Precautions) and Section 6 (Adverse Reactions) and states that UGN-101 should not be administered to patients with a GFR of < 30 mL/min.
15. The Instructions for Use provide guidance on measuring the pyelocalyceal volumes to mitigate risks of volume overdosing and injury to target organ and detailing how to instill UGN-101.
16. Training program for urologists with a Clinical Nurse Educator will be implemented on appropriate methods and techniques to mitigate risks of renal and urinary tract AEs.

Although there is insufficient data to support preferential use of the 5 Fr catheter, feedback from Investigators suggests that catheter diameter could impact technical ease of the procedure, and that in some cases they would substitute a 5 Fr catheter when technically

challenged during study drug administration. Thus there is a theoretical advantage to using the 5 Fr catheters conferred due to a smaller lumen size. Both 7 Fr and 5 Fr were used in Study UT001 and ability to select the appropriate sized catheter for the patient may confer additional advantage to the patient.

Due to administration of the treatment directly into the target organ, it was difficult for investigators to differentiate between relationship to the study drug and relationship to study procedure, particularly in the case of TEAEs from the Renal and urinary disorders SOC. For this reason, TEAEs were summarized by relationship to the study drug or relationship to procedure combined as well as by relationship to the study drug and relationship to procedure separately, as reported by investigators. In addition, to provide context in the absence of a comparator, a detailed analysis with regard to the known rate and severity of complications associated with ureteral catheterization in general practice has been performed from a comprehensive review of the literature (Ureteral Catheterization Complications White Paper). Potential risks identified as a result of this procedure included ureteral damage (stenosis), cystitis and other bladder irritation symptoms secondary to UUT instillation; an increased potential for UTI and pyelonephritis; as well as an increased potential for onset of renal insufficiency or deterioration of renal function. An ascertainment bias may apply, as it is likely that retrospective literature is subject to under reporting compared to the active reporting in a registrational clinical trial.

8.2.5.2. Risks of Bone Marrow Toxicity

The United States Prescribing Information (USPI; [Accord Healthcare 2014](#)) for mitomycin for injection contains a box warning indicating that bone marrow suppression, notably thrombocytopenia and leukopenia, is the most common and severe of the toxic effects of mitomycin, and that Hemolytic Uremic Syndrome, a serious complication of chemotherapy consisting primarily of microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure, has been reported in patients receiving systemic mitomycin.

Although local use via UUT instillation results in much lower systemic exposure than injection, AESIs potentially indicative of bone marrow suppression were selected from the SOC of Blood and lymphatic system disorders. The specific PTs identified were: Anemia, Leukocytosis, Leukopenia, Pancytopenia, and Thrombocytopenia.

While systemic administration of mitomycin is commonly associated with bone marrow toxicity (64.4%), a smaller proportion of patients in this study (21.1%, 15 patients) had laboratory abnormalities potentially indicative of bone marrow suppression. The majority of these events were mild in severity, and none were life threatening or fatal. The occurrence of these events in this study is not unexpected given the mechanism of action of mitomycin, although the frequency was lower than would be expected with systemic administration. The patient experience with each of the specific PTs identified as AESIs potentially indicative of bone marrow suppression is summarized below:

The most frequent were AESIs of Anemia (9 patients), all of which were reported as mild to moderate in severity and as non-serious. These were likely due to multiple etiologies in this patient population, as reflected by the assessment of relatedness to treatment (only 1 patient had an event that was considered to be definitely related).

The next most frequent were AESIs of Leukopenia (4 patients), all of which were reported as mild in severity and as non-serious. Only 1 patient had an event that was considered to be definitely related. In patients with normal white blood cell counts at baseline, the worst shift was to Grade 2 in 2 patients. In addition, 1 patient each shifted from Grade 1 at baseline to Grade 2 during the study and from Grade 2 at baseline to Grade 3 during the study. All 4 patients with leukopenia recovered during the study, and no patients terminated from treatment due to this AESI.

Overall, 3 patients experienced AESIs of Thrombocytopenia. This AESI was reported as severe in 2 cases and non-serious in all 3 cases. All 3 patients had events that were considered to be definitely related. During the study, the worst shifts were to Grade 3 in 1 patient with normal platelet counts at baseline and in 1 patient with a Grade 1 decrease at baseline. All 3 patients with thrombocytopenia recovered during the study, and 1 patient terminated from treatment due to this AESI.

Overall, 3 patients experienced AESIs of pancytopenia, and in 1 case it was reported as severe and was an SAE. One patient had an event that was considered to be definitely related. All 3 patients with pancytopenia recovered during the study, and no patients terminated from treatment due to this AESI.

In addition, 1 patient experienced an AESI of Leukocytosis that was mild, not related to treatment, and non-serious. The patients recovered during the study and did not terminate treatment due to this AESI.

A contraindication is listed in the label for patients with thrombocytopenia, coagulation disorder, or increased bleeding tendencies. Risks of bone marrow toxicity are covered in labeling in Section 5 (Warnings and Precautions) and Section 6 (Adverse Reactions) and states that platelet count, white blood cell count differential, and hemoglobin should be monitored prior to each treatment, and that the occurrence of a platelet count below 100,000/mm or a white blood cell count below 4,000/mm or a progressive decline in either is an indication to withhold further treatment until blood counts have recovered above these levels.

The FDA's Assessment:

Ureteral Obstruction:

FDA agrees with the Applicant that ureteral inflammation and stenosis is a known complication of upper tract instrumentation. In the absence of a randomized trial, it is unknown how the incidence of all ureteric obstruction events, and particularly high-grade events, compares between UGN-101 administration and alternative endoscopic therapies for LG-UTUC such as

laser ablation.

Ureteric Obstruction (Grouped Term), includes ureteric stenosis, hydronephrosis, pelvi-ureteric obstruction, urinary tract obstruction, ureteric obstruction, and obstructive uropathy; and was observed in 41 (58%) patients on UT001, including Grade 3 (12 patients; 17%). No Grade 4 or 5 were observed. The median time to first onset was 72 days (range: 15-462 days). Ureteric obstruction did not resolve or resolved with sequelae in 51% (21/41) of these patients. Of the 41 patients who experienced ureteric obstruction, seven (17%) experienced Grades 1-2 increase in serum creatinine. Intervention included ureteral stent placement (34 patients), balloon dilatation (15 patients), nephroureterectomy (2 patients), and other (11 patients). In the 36 patients who required ureteral stent placement, the median duration of indwelling stents was 51 days (range: 1-292). Prolonged indwelling stent duration may increase the risk of complications such as infection, migration, stent-related symptoms, and encrustation leading to lithiasis. Two patients ((b) (6)) underwent nephroureterectomy for ureteric obstruction.

Given the high incidence of ureteric obstruction that may require intervention and the potential for impact on renal function in a frail and elderly population with limited renal reserve, ureteral obstruction was included as a Warning and Precaution in Section 5 of the USPI.

Bone Marrow Suppression:

Mitomycin is an alkylating agent that causes frequent bone marrow suppression and cytopenias when administered systemically. The systemic exposure to mitomycin via UGN-101 pyelocalyceal administration is expected to be <1% of that expected via systemic exposure. Clinically significant cytopenias were rare on UT001 with 0%, 2.8%, and 2.8% incidences of Grade 3 or greater anemia, lymphopenia, and thrombocytopenia respectively. Two patients experienced Grade 3 thrombocytopenia, one of whom developed concomitant Grade 3 neutropenia. In neither patient was there observed gross extravasation of UGN-101 or evidence of upper urinary tract or bladder perforation. Bone marrow suppression will be included as a Warning and Precaution in Section 5 with emphasis on ensuring that health care providers obtain blood counts prior to each UGN-101 administration. Additionally, upper urinary tract or bladder perforation will be included as a contraindication for use.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position: Not Applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

The impact of age, gender, and BMI on the incidence of treatment-emergent AEs and serious AEs was assessed. These analyses did not reveal an impact of these factors on AE incidence.

Post-marketing surveillance of injectable mitomycin use has indicated that older patients may be more susceptible to hypersensitivity reactions. In Study UT001, 75% of the treated patients were aged 65 years or older and hypersensitivity reactions to UGN-101 were infrequent, mild to moderate in severity, and self-limiting. The method of administration of UGN-101 (via ureteral catheter) is expected to mitigate systemic effects as systemic exposure is greatly reduced.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. The majority of the studied population in OLYMPUS was >70 years. No significant differences in safety were observed for older vs younger patients.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

Not Applicable.

The FDA's Assessment:

See Section 5.5.3. The Applicant has relied on prior explorations of carcinogenicity of mitomycin. No additional carcinogenicity studies were performed for this NDA.

Human Reproduction and Pregnancy

The Applicant's Position:

Study UT001 excluded patients who were pregnant (positive serum pregnancy test), planning to become pregnant during the study period, breast-feeding, or were of childbearing potential and not practicing reliable contraception. Per the RLD labeling, the safe use of mitomycin in pregnant women has not been established, teratological changes have been noted in animal studies, and the effect of mitomycin on fertility is unknown.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Safety has not been established in pediatric patients. Study UT001 did not enroll any pediatric patients.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Due to the low systemic exposure to mitomycin when administered via instillation, overdose is not considered to be a significant risk. Abuse is unlikely due to the route of administration, and there were no AEs reported that were indicative of drug withdrawal during Study UT001. These are not known risks with mitomycin for injection, even at much higher levels of exposure.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Additionally, urinary tract perforation is labeled as a contraindication for UGN-101 administration, which is intended to reduce the risk of potential systemic exposure.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The Applicant has provided Instructions for Use that provide adequate guidance to the pharmacist preparing UGN-101 and Instructions for Administration that provide adequate guidance to the administering urologist. The FDA does not expect that UGN-101 will be administered in settings without the resources to address potential complications such as ureteral obstruction. While patients enrolled onto clinical trials such as OLYMPUS are frequently healthier than the general population, FDA does not expect that safety in the post-marketing setting will appreciably differ from the clinical trial setting.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Analysis of UGN-101 provided the primary evidence of safety. Prior small studies with different mitomycin concentrations and/or disease settings were not considered supportive. Limited data from compassionate use trials provided supportive evidence regarding long-term safety of UGN-101, however these data were not rigorously controlled or collected. Overall, the safety profile of UGN-101 appears acceptable for the treatment of LG-UTUC, a serious condition with limited alternative treatment options that may involve endoscopic resection, if feasible, or RNU.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

In general, there were no notable statistical issues with the study design, statistical analysis plan, or efficacy results for the UT001 study. We reiterate that no inferential procedures can be used to evaluate results from this single arm study. Instead, the efficacy evaluation was based on the magnitude of complete response rate and adequate durability of response.

The study showed a CR in 41 (58%) of the 71 patients (95% CI: 45%, 69%) following 6 weekly instillations of mitomycin. Based on DCO date of 18 December 2019, the median duration of

response was not reached (range: 0, 18.8+ months). Among the 41 patients who achieved a CR at PDE, 19 (46%) remained in CR at the 12 months post-PDE visit, which was pre-specified as the final study assessment visit.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the results of the ongoing single arm trial, OLYMPUS, UGN-101, a locally instilled mitomycin-based formulation has demonstrated a favorable risk benefit profile in patients with LG-UTUC, who may not have treatment options other than radical nephrectomy.

Efficacy assessment is based on the CR rate and durability of response. A CR was achieved in 58% of patients at the 3-month assessment. With 9 patients with ongoing follow-up in CR whose 12-month response status had not yet been assessed or determined, 19 (46%) patients continued in CR at the 12-month follow-up assessment after CR. Median duration was not reached by the time of data cut-off. Some longer durations of response were also reported in the Expanded Access Programs.

The safety profile of UGN-101 in patients with LG-UTUC is acceptable. The size of the safety database and duration of exposure of UGN-101 in UT001 was limited but sufficient to characterize the safety of UGN-101 for the treatment of a serious condition. The proportion of patients who experienced severe adverse events or permanently discontinued treatment due to an adverse event was relatively small and adverse events were generally local and did not reflect systemic exposure. Ureteric obstruction was the most common adverse event, but rarely lead to significant renal dysfunction, and was manageable with local interventions such as ureteral stenting. However, duration of stenting could be prolonged, which could lead to long-term issues such as infection.

We do not identify any issues that would preclude approval. Our recommendation is for the approval of UGN-101 for the treatment of patients with LG-UTUC. A post-marketing commitment to better characterize the response duration and risk for progression as well as the incidence of RNU was agreed upon with the applicant.

X

X

Primary Statistical Reviewer

Statistical Team Leader

X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No advisory committee discussion or consultations external to the FDA were deemed necessary for this NDA.

10 Pediatrics

The Applicant's Position:

LG UTUC is a cancer typically seen only in an adult population. As an Orphan Designated Drug Product, UGN-101 is exempt from the requirements of the Pediatric Research Equity Act (PREA). The NDA contained a request for a waiver from the requirements of PREA.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

11 Labeling Recommendations

The Applicant's Position:

There are currently no changes to the proposed labeling submitted with the initial application.

The FDA's Assessment:

The FDA's labeling revisions to the applicant's proposed labeling are included in Table 32.

Table 31. Summary of Significant Labeling Changes for NDA 211728 Jelmyto

<u>Section</u>	<u>Applicant's Proposed Labeling</u>	<u>FDA's Labeling Revisions</u>
<u>Highlights</u>		Under Warnings and Precautions, added "Embryo-Fetal Toxicity: Can cause fetal harm. Advise of potential risk to a fetus and to use effective contraception. (5.3, 8.1, 8.3)" and removed "(b) (4)" Under Use in Specific Populations, added "Lactation: Advise not to breastfeed. (8.2)" Under Adverse Reactions, revised to include adverse reactions occurring in ≥20% of treated patients.
<u>1 Indications and Usage</u>	JELMYTO™ (b) (4) is indicated for the treatment of low-grade Upper Tract Urothelial Cancer (UTUC).	JELMYTO™ is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

<u>2 Dosage and Administration</u>	Section 2.1 Recommended Dosage (b) (4)	Section 2.1 Important Administration Instructions See the Instructions for Administration provided separately. JELMYTO is for pyelocalyceal use only. JELMYTO is not for intravenous use, topical use, or oral administration. Prior to every instillation, instruct the patient to take 1.3 g of sodium bicarbonate orally the evening prior to, the morning of, and 30 minutes prior to the instillation procedure (total of 3.9 g). General anesthesia, local anesthesia, sedation, prophylactic antibiotics and/or antihistamines may be used at the discretion of the treating urologist. If the patient is to be anesthetized, advise the patient not to take sodium bicarbonate within 30 minutes prior to the treatment. Consider withholding diuretics one day prior to instillation until 4 hours post-instillation. When instilling JELMYTO, the entire syringe must be emptied within one minute. Advise patients that JELMYTO
	Section 2.2 Administration Instructions	

		may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use. Section 2.2 Recommended Dosage The dose of JELMYTO to be instilled is 4 mg per mL via ureteral catheter or nephrostomy tube, with total instillation volume based on volumetric measurements using pyelography, not to exceed 15 mL (60 mg of mitomycin). Instill JELMYTO once weekly for six weeks. For patients with a complete response 3 months after JELMYTO initiation, JELMYTO instillations may be administered once a month for a maximum of 11 additional instillations.
<u>4 Contraindications</u>	Jelmyto is contraindicated in patients (b) (4) JELMYTO is contraindicated	JELMYTO is contraindicated in patients with: perforation of the bladder or upper urinary tract.

		(b) (4)	
<u>5 Warnings and Precautions</u>	5.1	(b) (4) (b) (4)	Revised Section 5.1 Ureteric Obstruction to use Grouped Term, “Ureteric Obstruction”; to include analysis using the grouped term; to add information regarding onset, duration, and interventions; to revise language to conform with current labeling practices Deleted (b) (4) Revised Section 5.3 Bone Marrow Suppression. (b) (4) Deleted (b) (4) Added Section 5.3 Embryo-Fetal Toxicity to inform that based on mechanism of action and findings in animals, Jelmyto can cause fetal harm. Added duration of contraception use as described in section 8 below
	5.3 Bone Marrow	(b) (4) (b) (4)	

	(b) (4)	
<u>6 Adverse Reactions</u>	Did not include Laboratory Abnormalities	Added discussion on serious adverse reactions, discontinuation due to adverse reaction, dosage interruptions due to an adverse reaction, and common adverse reactions. Revised Table 1 to use grouped terms when available (defined in footnotes) Included selected clinically relevant adverse reactions with incidence 2% to <10%. Added Table 2: Select Laboratory Abnormalities

<u>7 Drug Interactions</u>		Deleted (b) (4)
<u>8 Use In Specific Populations</u>	Section 8.1 Pregnancy (b) (4)	Edited statements to be consistent with current PLLR labeling practices in OOD.
		(b) (4)
	Section 8.2 Lactation (b) (4)	Edited statements to be consistent with current labeling practices in OOD and to advise women not to breastfeed during treatment with Jelmyto and for 1 week following the last dose.
		Under Section 8.3, added subheading "Pregnancy Testing" and "Verify

		pregnancy status in females of reproductive potential prior to initiating JELMYTO. Added subheading “Contraception” and “Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for (b) (4) months following the last dose.”
<u>12 Clinical Pharmacology</u>	Section 12.1 Mechanism of Action (b) (4)	Edited statements to align with the listed drug. “Mitomycin inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.”
<u>13 Nonclinical Toxicology</u>	In Section 13.1, the Applicant summarized results from (b) (4) (b) (4)	Deleted statements. The referenced publication was not considered relevant as (b) (4) (b) (4)

		were not needed to support a marketing application for Jelmyto for the proposed indication. (b) (4) (b) (4)
<u>14 Clinical Studies</u>		Revised efficacy data tables and text. Deleted (b) (4). Added Efficacy Results with Complete Response Rate and Duration of Response.
<u>17 Patient Counseling Information</u>		Added “Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare providers of a known or suspected pregnancy” Added duration of contraception and time period to avoid breastfeeding to be consistent with section 8 as above.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

No REMS is recommended.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

Given the immaturity of the OLYMPUS study, the following post-marketing commitment was agreed upon with the applicant:

Provide annual updates for the duration of response (median and range) for all patients with ongoing complete responses enrolled in clinical trial OLYMPUS. These updates should include information regarding incidences of recurrence of low-grade upper tract urothelial carcinoma (UTUC), incidence of/progression to high-grade UTUC, and incidence of nephroureterectomy. Annual updates should continue for five years or until all patients have either experienced recurrence, death, or been lost to follow-up.

Annual Report #1:	04/2021
Annual Report #2:	04/2022
Annual Report #3:	04/2023
Annual Report #4:	04/2024
Annual Report #5:	04/2025

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

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influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

The main toxicology study is disclosed in Section 5.5.

The FDA's Assessment:

FDA agrees that all nonclinical information is included in Section 5.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	George Ching-Jey Chang	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☐ Approved
Signature: Ching Jey G. Chang -S Digitally signed by Ching Jey G. Chang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000350983, cn=Ching Jey G. Chang -S Date: 2020.04.09 13:10:28 -04'00'				
Nonclinical Team Leader	Tiffany Ricks	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000497170, cn=Tiffany K. Ricks -S Date: 2020.04.09 13:26:03 -04'00'				
Clinical Pharmacology Reviewer	Catharine Bulik	OCP/DCPV	Sections: 6	Select one: ☒ Authored ☐ Approved
Signature: Catharine C. Bulik -S Digitally signed by Catharine C. Bulik -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002702169, cn=Catharine C. Bulik -S Date: 2020.04.09 13:27:55 -04'00'				
Clinical Pharmacology Team Leader	Pengfei Song	OCP/DCPV	Sections:6	Select one: ☒ Authored ☒ Approved
Signature: Pengfei Song -S Digitally signed by Pengfei Song -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Pengfei Song -S, 0.9.2342.19200300.100.1.1=2000464900 Date: 2020.04.10 14:52:13 -04'00'				
Clinical Reviewer	Dow-Chung Chi	OOD/DO1	Sections: 1-4, 7-10, 12-13	Select one: ☒ Authored ☐ Approved
Signature: Dow-chung Chi -S Digitally signed by Dow-chung Chi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dow-chung Chi -S, 0.9.2342.19200300.100.1.1=2001243305 Date: 2020.04.09 15:24:37 -04'00'				

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Statistical Reviewer and Team Leader	Mallorie Fiero	OB/DBV	Sections: 7,8,11	Select one: ☒ Authored ☒ Approved
	Signature: Mallorie H. Fiero -S Digitally signed by Mallorie H. Fiero -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002084959, cn=Mallorie H. Fiero -S Date: 2020.04.09 13:47:25 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Daniel Suzman	OOD/DO1	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature:			
Division Director (OB)	Shenghui Tang	OB/DBV	Sections: 7,8,11	Select one: ☐ Authored ☒ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2020.04.09 12:59:25 -04'00'			
Deputy Division Director (Clinical)	Amna Ibrahim	OOD/DO1	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature:			

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/s/

FATIMA M RIZVI
04/14/2020 02:53:25 PM

DANIEL L SUZMAN
04/14/2020 02:56:14 PM

AMNA IBRAHIM
04/14/2020 03:03:35 PM

MEMORANDUM

Date: April 14, 2020

From: Daniel Suzman, M.D., Division of Oncology 1

Cross-Disciplinary Team Lead

Re: NDA 211728, UGN-101 (JELMYTO)

The clinical review is complete and has been added to the NDA 211728 assessment aid review. My recommendation for this application is approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DANIEL L SUZMAN
04/14/2020 01:05:22 PM

Clinical Reviewer Memorandum

Application Type	NDA
Application Number(s)	211728
Priority or Standard	Priority
Submit Date(s)	October 18, 2019
Received Date(s)	October 18, 2019
PDUFA Goal Date	April 18, 2020
Division/Office	DO1/OOD/OND/CDER
Established Name	Mitomycin gel
(Proposed) Trade Name	JELMYTO
Pharmacologic Class	Alkylating drug
Applicant	UroGen Pharma, Inc.
Recommendation on Regulatory Action	Priority Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of low-grade Upper-Tract Urothelial Cancer

The Clinical Review is complete, and has been added to the NDA integrated review document. My recommendation for this application is Approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DOW-CHUNG CHI
04/14/2020 02:48:07 PM



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES - MEMO

NDA/BLA #: 211728
Supplement #:
Drug Name: Mitomycin gel
Indication(s): Treatment of low-grade upper-tract urothelial cancer
Applicant: UroGen Pharma, Inc.
Date(s): Receipt: October 18, 2019
PDUFA date: April 18, 2020
Review Priority: Priority

Biometrics Division: DBV
Statistical Reviewer: Wei Zhang, PhD
Concurring Reviewers: Mallorie Fiero, PhD Team Leader (Acting)
Medical Division: Division of Oncology 1
Clinical Team: Dow-Chung Chi, MD
Daniel Suzman, MD, Team Leader
Amna Ibrahim, MD, Deputy Division Director
Project Manager: Fatima Rizvi

The statistical review is complete and has been incorporated into the NDA integrated review document, which will be uploaded to DARRTS when it is finalized. Refer to the NDA integrated review document, for additional details on statistical review issues for the NDA. From a statistical standpoint, this NDA is acceptable to support approval.

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/s/

MALLORIE FIERO
04/09/2020 01:09:15 PM

SHENGHUI TANG
04/09/2020 01:10:57 PM

Office of Clinical Pharmacology Review

Application Number	NDA 211728 (SDN 0008)
Submission Date	10/18/2019
Submission Type	505(b)(2)
Submission link (path)	\\cdsesub1\evsprod\NDA211728\0008
Product Name	UGN-101
Route of Administration	Gel for instillation
Proposed Indication(s)	For the treatment of low-grade upper tract (b) (4) urothelial carcinoma (LG-UTUC, (b) (4))
Sponsor	UroGen Pharma, Inc.
Primary Reviewer	Catharine Bulik
Team Leader	Pengfei Song

The Clinical Pharmacology review of NDA211728 is complete and has been added to the NDA Assessment Aid. Clinical pharmacology recommendation for NDA211728 is approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CATHARINE C BULIK
04/09/2020 11:38:03 AM

PENGFEI SONG
04/09/2020 11:42:50 AM

MEMORANDUM

DATE: April 1, 2020
TO: File for NDA 211728 JELMYTO (mitomycin)
RE: Pharmacology/Toxicology NDA Evaluation
FROM: C.J. George Chang, DVM, PhD (Nonclinical Reviewer)
Division of Hematology Oncology Toxicology (DHOT) for Division of Oncology 1 (DO1)
THROUGH: Tiffany Ricks, PhD (Nonclinical Team Leader)

The Nonclinical Primary Review for NDA 211728 is complete and has been added to the NDA Multidisciplinary Review and Evaluation (Assessment Aid). My recommendation for this application is approval.

The Nonclinical Secondary Review is complete. My recommendation for this application is approval.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHING-JEY G CHANG
04/01/2020 09:55:38 AM

TIFFANY RICKS
04/01/2020 09:56:41 AM