1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3, Single-arm, Multicenter Study to Evaluate the Efficacy and Safety of UGN-104, a Novel Formulation of UGN-101, for the Treatment of Patients With Low-grade Upper Tract Urothelial Cancer (LG-UTUC)

Short Title: A Phase 3 Single-arm Study of UGN-104 for the Treatment of LG-UTUC

Rationale: JELMYTO (mitomycin) for pyelocalyceal solution (product code UGN-101) was approved by the US Food and Drug Administration (FDA) for the treatment of adult patients with LG-UTUC on April 15, 2020. UroGen is developing UGN-104, a reformulation of the mitomycin lyophilized powder in UGN-101, to simplify the reconstitution procedure and considerably shorten the manufacturing process. This is accomplished by using a solvent system of tert-Butanol and water for injection (WFI) for lyophilized mitomycin bulk solution preparation rather than WFI as a single solvent and replacing the bulking agent mannitol with urea due to the low solubility of mannitol in the solvent mixture and the adequate solubility of urea. The higher solubility of mitomycin in the tert-Butanol:WFI mixture allows for an increase in dose per vial from 40 mg to 80 mg (simplifying preparation of UGN-104 admixture) and significantly reduces the lyophilization cycle duration from 20 days to approximately 3 days, increasing the manufacturing capacity of mitomycin.

UroGen has demonstrated that UGN-104 and UGN-101 are comparable in their critical quality attributes, and comparative dissolution analysis of admixture prepared from the original and reformulated products showed that reformulated mitomycin has no effect on the in vitro dissolution profile. The estimated increase in urea concentration in the urine following treatment with reformulated mitomycin is expected to be within the normal physiological urea concentration variability.

Since mitomycin for pyelocalyceal solution is locally administered in the upper tract, the systemic exposure of mitomycin is minimal and a traditional bioequivalence determination between the original and reformulated products is not feasible. Therefore, UroGen is conducting a clinical endpoint study in adult patients with LG-UTUC using the new formulation (UGN-104) to establish the similarity of the safety and efficacy profiles of the two products. The data from this study will be compared with the results from Phase 3 Study UT001 using the original formulation (UGN-101).

Objectives and Endpoints

Objective	Endpoint
Primary	
• To evaluate the tumor ablative effect of UGN-104, a novel formulation of UGN-101, in patients with LG-UTUC.	• CRR, defined as the proportion of patients who achieve CR at the PDE Visit (5 ± 1 weeks after the sixth instillation of UGN-104) as determined by wash urine cytology, ureteroscopy, and for cause biopsy.
Secondary	
• To evaluate the durability of response with respect to DOR and DCR rate at scheduled disease assessment time points.	• DOR in patients who achieved CR at the PDE Visit, defined as the time from the date of evidence of CR at the PDE Visit to the earliest date of recurrence, progression or death as determined using the date of cytology, ureteroscopy, or for cause biopsy, or death due to any cause, whichever occurs first. • DCR rate at scheduled disease assessment time points, defined as the proportion of patients who achieve CR at the PDE Visit and maintain CR (ie, no detectable disease) up to that particular follow-up disease assessment.
• To evaluate the safety and tolerability of UGN-104 in patients with LG-UTUC.	• Safety and tolerability will be evaluated through the reporting of AEs, including SAEs and AESIs, and through standard clinical and laboratory tests (eg, hematology and chemistry, urinalysis, physical examination, and vital signs).
• To assess the PK profile of mitomycin in plasma in a subgroup of patients treated with UGN-104.	• Concentration data and PK parameters (C_{max}, t_{max}, AUC, $t_{1/2}$, and λ_Z).
Exploratory	
• To assess the effect of UGN-104 on PRO measures including quality of life, treatment satisfaction, and PGI-C.	• Changes from baseline in patient scores on the QLQ-C30 and TSQM questionnaires. • Proportion of study participants reporting improvement at end of study on the PGI-C. The proportion reporting improvement over time will also be assessed to understand when change occurred.

AE = adverse event; AESI = adverse event of special interest; AUC = area under the concentration-time curve; C_{max} = maximum plasma concentration; CR = complete response; CRR = complete response rate; DCR = durable complete response; DOR = duration of response; LG-UTUC = low-grade upper tract urothelial cancer; PDE = primary disease evaluation; PK = pharmacokinetic(s); PGI-C = patient global impression of change; PRO = patient-reported outcome; QLQ-C30 = Quality of Life Questionnaire for Cancer Patients; SAE = serious adverse event; $t_{1/2}$ = terminal half-life; t_{max} = time to maximum plasma concentration; TSQM = Treatment Satisfaction Questionnaire for Medication; λ_Z = elimination rate constant.

Overall Design

This Phase 3, single-arm, multicenter study will evaluate the efficacy and safety of UGN-104, a novel formulation of UGN-101, instilled in the upper urinary tract (UUT) of patients with LG-UTUC.

Patients who provide informed consent will undergo a Screening Visit to determine eligibility. Eligible patients will be treated with UGN-104 once weekly for 6 weeks (a total of 6 doses). Every effort will be made to ensure ≥ 50% of patients receive UGN-104 via antegrade administration. A general description of study visits is summarized below.

	Visit	**Timeline**
All Patients	Screening	Up to 6 weeks before the start of treatment
	Instillations 1-6 (Visit 1 to Visit 6)	Once weekly for 6 weeks
	Safety laboratory assessments (Visits 7 and 8)	1 week and 3 weeks after the sixth instillation
	Primary disease evaluation (PDE) (Visit 9)	5 ± 1 weeks after the sixth instillation
Patients With Complete Response at PDE	Optional maintenance instillations (Visit 10 to Visit 20)	Once monthly for 11 months
	Follow-up visits (Visits 12, 15, 18, and 21)	3, 6, 9, and 12 months after the PDE Visit

Efficacy will be assessed by the complete response rate (CRR) at the Primary Disease Evaluation (PDE) Visit occurring 5 ± 1 weeks after the sixth instillation. Response will be determined based on UUT wash urine cytology followed by visual evaluation using ureteroscopy (URS) (appearance, number, size, and location of any visible lesions), and histopathology of any lesions. A biopsy shall be performed for all remaining lesions where technically feasible.

Patients who have a complete response (CR) at the PDE Visit, defined as having no detectable disease (NDD), will enter the Follow-up Period of the study. During the Follow-up Period, patients may receive UGN-104 as maintenance treatment at the discretion of the investigator. The maintenance regimen is once monthly for 11 months (a total of 11 doses) and should start as soon as possible (no longer than 3 weeks) after CR is determined at the PDE Visit. All patients in the Follow-up Period, regardless of whether they receive maintenance treatment, will return to the clinic every 3 months for evaluation of response and will remain on study for 12 months after the PDE Visit or until disease recurrence, disease progression, or death, whichever occurs first.

Patients who have a non-complete response (NCR) at the PDE Visit will be considered to have completed the study.

Safety will be evaluated based on review of adverse events (AEs) and changes from baseline in laboratory assessments, physical examination findings, and vital signs. All safety data will be reviewed on an ongoing basis by the sponsor, including close review and follow up of any unexpected AEs assessed as related to UGN-104 and qualified as Grade 3 or 4 according to the latest version of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) at the start of the study.

Inclusion Criteria

1. Provide written informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2. Patient must be ≥ 18 years of age at the time of informed consent.

3. Naive or recurrent patients with LG, non-invasive UTUC in the pyelocalyceal system, with the following disease characteristics:

   a. At least 1 measurable papillary LG tumor, evaluated visually, ≤ 15 mm. The largest lesion should not exceed 15 mm. Debulking to ≤ 15 mm is permitted.

   b. Biopsy taken from at least 1 tumor located above the ureteropelvic junction revealing LG urothelial carcinoma (UC). Patients who have been biopsied within 8 weeks before Screening for this study and shown to have LG UC may have these historical biopsies used for enrollment into the study and do not require repeat biopsy during Screening.

   c. Patient should have at least 1 remaining papillary LG tumor evaluated visually with a diameter of at least 5 mm post-biopsy.

   d. Wash urine cytology sampled from the pyelocalyceal system documenting the absence of high-grade (HG) UC, diagnosed not more than 8 weeks before Screening.

   e. Patients with bilateral LG-UTUC may be enrolled if at least 1 side meets the inclusion criteria for the study and if the other kidney does not require further treatments. (The disease in the other kidney must be completely ablated before receiving treatment in the study.)

      Note: If both upper tracts meet inclusion criteria, the treating urologist in consultation with the sponsor's medical monitor can decide which side to treat in the study. The pyelocalyceal system not under study must be free of cancer before the first instillation on the side to be treated in the study.

4. Patients with Eastern Cooperative Oncology Group (ECOG) performance status < 3 (with Karnofsky > 40) (see Appendix 1).

5. Patients with life expectancy > 24 months at time of Screening.

6. Patients must have adequate organ and bone marrow function as determined by the following routine laboratory tests:

   a. Leukocytes ≥ 3,000/µL (≥ 3×10^9/L).

   b. Absolute neutrophil count ≥ 1,500/µL (≥ 1.5×10^9/L).

   c. Platelets ≥ 100,000/µL (≥ 100×10^9/L).

   d. Hemoglobin ≥ 9.0 g/dL.

   e. Total bilirubin ≤ 1.5 × upper limit of normal (ULN).

f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN.

g. Alkaline phosphatase ≤ 2.5 × ULN.

h. Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min.

7. Patient has no active urinary tract infection (UTI) as confirmed by urine culture or urinalysis.

   Note: In case of a symptomatic UTI the patient will be treated with antibiotics and the instillation will be postponed until resolution. In the case of asymptomatic bacteriuria, the use of prophylactic antibiotics and postponement of treatment is at the discretion of the PI.

8. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for clinical study participants.

   Female patients of childbearing potential (defined as premenopausal women who have not been sterilized) and male patients with female partners of childbearing potential must agree to use 2 acceptable forms of effective contraception from enrollment through 6 months post-treatment. Sexually active male patients must agree to use a condom during intercourse for at least 48 hours after each instillation.

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

   * Sexual abstinence is defined as refraining from intercourse from enrollment through 6 months post treatment. Periodic abstinence (calendar, symptothermal, post-ovulation methods) is NOT an acceptable method of contraception.

Exclusion Criteria

1. UC specific exclusions:

   a. Patient received Bacillus Calmette-Guérin (BCG) treatment for UC during the 6 months before enrollment.

   b. The patient has untreated concurrent UC in locations other than the target area (unless treated and resolved during Screening); ie, ureteral and lower urinary tract tumors must be completely ablated before entry.

   c. Patient has a history of carcinoma in situ (CIS) in the urinary tract.

   d. Patient has a history of invasive UC in the past 5 years.

   e. Patient has a history of HG papillary UC in the urinary tract in the past 2 years.

2. Patient is actively being treated or intends to be treated with systemic chemotherapy during the duration of the study.

3. Any other malignancy diagnosed within 2 years before enrollment with the exception of:
    a. Basal or squamous cell skin cancers.
    b. Noninvasive cancer of the cervix.
    c. Any other cancer deemed to be of low risk for progression or patient morbidity during the study period in the opinion of the investigator.
4. Patient with urinary obstruction such that there is an inability to deliver the study treatment to the pyelocalyceal system either via ureteral catheter (retrograde administration) or nephrostomy tube (antegrade administration).
5. Known allergy or sensitivity to any component of the study treatment (including excipients) that in the investigator's opinion cannot be readily managed.
6. Patient has an intractable bleeding disorder (eg, coagulation factors deficiencies, Von Willebrand disease).
7. Patient is currently receiving any other investigational product, has participated in a research protocol involving administration of an investigational product in the past 30 days, or plans to participate in a research protocol involving administration of an investigational product during study conduct.
8. Patient was previously treated with JELMYTO (product code UGN-101) for UTUC.
9. Women who are pregnant (positive urine or serum pregnancy test), planning to become pregnant during the study period, or who are breastfeeding are not eligible to enroll.
10. Patient has any other medical or mental condition(s) that make(s) his/her participation in the study unadvisable in the opinion of the investigator.
11. Where applicable per country regulation, the patient must not be currently committed to an institution by virtue of an order issued by either judicial or administrative authorities.

Intervention Groups and Duration: Patients will receive UGN-104 once weekly for 6 weeks (a total of 6 doses). Patients will receive all 6 of these instillations using the same route (either antegrade or retrograde). Patients who have a CR at the PDE Visit will enter the Follow-up Period and may receive UGN-104 as maintenance treatment once monthly for 11 months (a total of 11 doses) at the discretion of the investigator. During maintenance treatment, patients are not required to receive UGN-104 via the same administration route (antegrade or retrograde) as used during the Treatment Period. The route of administration for maintenance dosing may be selected at the investigator's discretion, based on patient-specific considerations and clinical judgment.

The dose of UGN-104 to be instilled is 4 mg mitomycin per 1 mL sterile hydrogel via ureteral catheter (retrograde administration) or nephrostomy tube (antegrade administration), with total