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)

Protocol Number: UT002

Compound: UGN-104 (mitomycin) for pyelocalyceal solution

Study Phase: 3

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

Sponsor Name: UroGen Pharma Ltd.

1 PROTOCOL SUMMARY

1.1 Synopsis

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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).

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.