Medical Information Request: ZUSDURI™ (mitomycin) for intravesical solution and the Phase 3 ENVISION Trial

Thank you for your question regarding the ENVISION trial (NCT05243550), a Phase 3, Single-Arm, Multicenter Study to Evaluate the Efficacy and Safety of ZUSDURI as Primary Chemoablative Therapy in Patients with Low Grade (LG) Non-Muscle Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence.

ZUSDURI™ is indicated for the treatment of adult patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC).

Background:

ENVISION is a Phase 3, single-arm, multinational study evaluating the efficacy and safety of ZUSDURI (UGN-102) as a primary chemoablative therapy in 240 patients with LG-IR-NMIBC across 56 sites in the United States and Europe.

Utilizing UroGen's proprietary sterile hydrogel technology, ZUSDURI is hydrogel-based formulation designed to enable longer exposure of bladder tissue to mitomycin. Based on patient-reported visibility of gel in urine post-treatment, ZUSDURI has a median dwell time of 5 hours with reports up to 24 hours. The reverse thermal properties of ZUSDURI allow for local administration of mitomycin as a liquid under chilled conditions, with subsequent conversion to a semisolid gel depot following instillation into the bladder.

Study Design:

- Patients enrolled in ENVISION were eligible to receive six once-weekly intravesical instillations of ZUSDURI.
- The ZUSDURI admixture for intravesical instillations contains 75 mg mitomycin in 56 mL admixture (1.33 mg/mL).
- All patients will return to the clinic approximately 3 months after the first instillation for determination of response to treatment. Assessment of response will be based on visual observation (white light cystoscopy), histopathology of any remaining or new lesions by central pathology lab (if applicable), and interpretation of urine cytology by central pathology lab.
- Patients confirmed to have a complete response (CR) at the 3-month Visit, defined as having no detectable disease (NDD) in the bladder, will enter the Follow-up Period of the study. Patients confirmed to have a non-complete response (NCR) will undergo Investigator designated standard of care (SOC) treatment of remaining lesions and then enter the Follow-up Period of the study.
- During the Follow-up Period, patients will return to the clinic every 3 months for up to 24 months (i.e., 27 months after the first instillation) for evaluation of response. Patients who remain disease free at the 27-month Visit will continue to return to the clinic every 6 months for up to an additional 36 months (i.e., 63 months after the first instillation) or until disease recurrence, disease progression, death, or the study is closed by the Sponsor, whichever occurs first.
- Patients confirmed to have a disease recurrence during the Follow-up Period or a disease progression at the 3-month Visit or during the Follow-up Period will undergo Investigator designated SOC treatment and have a separate End of Study (EOS) Visit performed. The timing of the EOS Visit will be approximately 3 months after SOC treatment of disease recurrence or progression.

Patient Population:

Inclusion Criteria	Exclusion Criteria
1. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and the protocol. 2. Patient who has LG-NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks before Screening.	1. Received Bacillus Calmette-Guérin (BCG) treatment for urothelial carcinoma (UC) within previous 1 year. 2. History of HG bladder cancer (papillary or carcinoma in situ [CIS]) in the past 2 years.

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3. History of LG-NMIBC requiring treatment with transurethral resection of bladder tumors (TURBT). Note: This refers to a previous episode(s) and not to the current episode for which the patient is being screened. 4. Has intermediate risk disease, defined as having 1 or 2 of the following: ○ Presence of multiple tumors; ○ Solitary tumor > 3 cm; ○ Early or frequent recurrence (≥ 1 occurrence of LG-NMIBC within 1 year of the current diagnosis at the initial Screening Visit). 5. Negative voiding cytology for high grade (HG) disease within 8 weeks before Screening. 6. Has adequate organ and bone marrow function as determined by routine laboratory tests as below: ○ Leukocytes ≥ 3,000 per µL; ○ Absolute neutrophil count ≥ 1,500 per µL; ○ Platelets ≥ 100,000 per µL; ○ Hemoglobin ≥ 9.0 g/dL; ○ Total bilirubin ≤ 1.5 x upper limit of normal (ULN); ○ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × ULN; ○ Alkaline phosphatase (ALP) ≤ 2.5 × ULN; ○ Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min. 7. Has an anticipated life expectancy of at least the duration of the trial. 8. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Women of childbearing potential (defined as premenopausal women who have not been sterilized), including female patients and female partners of male patients, must be willing to use 2 acceptable forms of effective contraception from enrollment through 6 months post-treatment.	3. Known allergy or sensitivity to mitomycin that in the Investigator's opinion cannot be readily managed. 4. Clinically significant urethral stricture that would preclude passage of a urethral catheter. 5. History of: ○ Neurogenic bladder; ○ Active urinary retention; ○ Any other condition that would prohibit normal voiding. 6. Past or current muscle invasive bladder cancer (ie, T2, T3, T4) or metastatic UC. 7. Current tumor grading of T1. 8. Concurrent upper tract urothelial carcinoma (UTUC). 9. Evidence of active urinary tract infection (UTI) that in the Investigator's opinion cannot be treated and resolved prior to biopsy and/or administration of study treatment. 10. Is pregnant or breastfeeding. 11. Has an underlying substance abuse or psychiatric disorder such that, in the opinion of the Investigator, the patient would be unable to comply with the protocol. 12. History of prior treatment with an intravesical chemotherapeutic agent in the past 2 years except for a single dose of chemotherapy immediately after any previous TURBT. 13. Has participated in a study with an investigational agent or device within 30 days of enrollment. 14. Has previously participated in a study in which they received ZUSDURI. 15. Has any other active malignancy requiring treatment with systemic anticancer therapy (eg, chemotherapy, immunotherapy, radiation therapy). Superficial cancers such as cutaneous basal cell or squamous cell carcinomas that can be treated locally are allowed. 16. Has any other clinically significant medical or surgical condition that in the Investigator's opinion could compromise patient safety or the interpretation of study results.

Results:

Primary Endpoint: Complete Response (CR) at 3 months

- CR was the proportion of patients who achieved CR at the 3-month primary disease evaluation (PDE), as defined by cystoscopy, urine cytology, and for cause biopsy.

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- The ENVISION trial met its primary endpoint by demonstrating that patients treated with ZUSDURI had a 79.6% (95% CI: 73.9, 84.5) rate of complete response at 3 months following the initial treatment.

Key Secondary Endpoints:

- Duration of Response (DOR)
  - DOR was defined as time from first documented CR until the earliest date of recurrence, progression, or death.
  - As of the April 2024 data cut, of the patients that achieved a CR at 3 months, the probability of remaining in response 12-months after CR was 82.3% (95% CI: 75.9, 87.1, KM estimate). Median follow up time was 13.9 months.
  - As of the October 2024 data cut, of the patients that achieved a CR at 3 months, the probability of remaining in response 18-months after CR was 80.6% (95% CI: 74.0, 85.7; KM estimate). Median follow up time was 18.7 months.
  - The median DOR was not estimable due to the high number of patients remaining in complete response.
- Durable Complete Response (DCR)
  - DCR was defined as the observed percentage of patients who had maintained CR after achieving CR at 3 months.
  - As of the April 2024 data cut, 76.4% (95% CI 69.8 – 82.3) of patients who achieved a CR at 3 months maintained an observed CR after 12 months.

Other secondary endpoints currently ongoing include DOR up to 63 months and disease-free survival (DFS).

Safety:

- The safety profile for ZUSDURI in ENVISION was similar to other ZUSDURI studies, including OPTIMA II and ATLAS.
- The most common (≥10%) adverse reactions, including laboratory abnormalities, that occurred in patients treated with ZUSDURI were increased creatinine, increased potassium, dysuria, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, increased eosinophils, decreased lymphocytes, urinary tract infection, decreased neutrophils, and hematuria.
- Serious adverse reactions occurred in 12% of patients who received ZUSDURI, including urinary retention (0.8%) and urethral stenosis (0.4%). A fatal adverse reaction of cardiac failure occurred in 1 (0.4%) patient (0.4%) receiving ZUSDURI.
- Dosage interruption of ZUSDURI due to adverse reactions occurred in 10% of patients. Adverse reactions (≥ 2%) which required dosage interruption were urinary tract infection (2.5%) and dysuria (2.5%)
- Permanent discontinuation of ZUSDURI due to an adverse reaction occurred in 2.9% of patients, including 1.7% who discontinued due to a renal or urinary disorder.

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	UGN-102 (N = 240) / n (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Patients With Any TEAEs	**57 (23.8)**	**47 (19.6)**	**27 (11.3)**	**3 (1.3)**	**3 (1.3)[a]**	**137 (57.1)**
Dysuria	44 (18.3)	9 (3.8)	1 (0.4)	0	0	54 (22.5)
Hematuria	15 (6.3)	5 (2.1)	0	0	0	20 (8.3)
Urinary tract infection	6 (2.5)	10 (4.2)	1 (0.4)	0	0	17 (7.1)
Pollakiuria	12 (5)	4 (1.7)	0	0	0	16 (6.7)
Fatigue	9 (3.8)	4 (1.7)	0	0	0	13 (5.4)

	UGN-102 (N = 240) / n (%)
Patients With Any Treatment Related Grade 3 TEAEs	**2 (0.8)**
Urethral stenosis	1 (0.4)
Urinary retention	1 (0.4)

Post-hoc analysis of EORTC recurrence score subgroups (poster presented at ASCO-GU 2026):

The European Organisation for Research and Treatment of Cancer (EORTC) recurrence scores provide estimates of recurrence, after TURBT with or without intravesical treatment, based on baseline prognostic factors. Patients with recurrence scores of 1–4, 5–9, or 10–17, had a probability of recurrence at 1 year of 24%, 38%, or 61%, respectively.

In this post-hoc analysis, complete response (CR) at 3 months and duration of response (DOR) were calculated in patients grouped by EORTC recurrence scores of 1–4, 5–9, and 10–17 at baseline. EORTC recurrence scores were based on 3 factors: number of tumors, tumor size, and prior recurrence rate. Limitations include the small sample size in the 1-4 and 10-17 subgroups.

Baseline Characteristics of ENVISION Patients by EORTC Group

	EORTC Recurrence Score Group		
Characteristic	**1-4 (N=31)**	**5-9 (N=191)**	**10-17 (N=15)**
Mean Age, years (SD)	71.8 (10.6)	67.8 (11.7)	74.5 (10.1)
Male Sex, n (%)	17 (54.8)	118 (61.8)	10 (66.7)
Treatment Course, n (%)			
<6 instillations	3 (9.7)	7 (3.7)	1 (6.7)
6 instillations	28 (90.3)	184 (96.3)	14 (93.3)
Tumor Count, n (%)			
Single	24 (77.4)	16 (8.4)	0
Multiple	7 (22.6)	175 (91.6)	15 (100)
Tumor Burden,[a] n (%)	n=30	n=180	n=11
≤3cm	29 (96.7)	150 (83.3)	1 (9.1)
>3cm	1 (3.3)	30 (16.7)	10 (90.9)
Missing[b]	1 (3.2)	11 (5.8)	4 (26.7)

EORTC, European Organisation for Research and Treatment of Cancer; SD, standard deviation.

[a]Calculated as the sum of the longest diameters of the measurable lesions.

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[b]For missing data, percentages are computed using N as the denominator. For non-missing data, percentages are computed using the number of non-missing data as the denominator.

CR rate at 3 months was 83.9%, 81.2%, and 60% for patients with recurrence scores of 1–4, 5–9, and 10–17, respectively. The probability of remaining event-free at 24 months was 67.4%, 73.7%, and 66.7% for patients with scores 1–4, 5–9, and 10–17, respectively. The median duration of follow-up for each group is shown below; KM estimate of median DOR was not estimable for any group due to the low event rates.

Response Rate at 3 Months and Duration of Response by EORTC Group

	EORTC Recurrence Score Group		
Characteristic	**1-4 (N=31)**	**5-9 (N=191)**	**10-17 (N=15)**
CR at 3 Months, n (%)	26/31 (83.9)	155/191 (81.2)	9/15 (60)
CRR (95% CI)	83.9 (66.3, 94.5)	81.2 (74.9, 86.4)	60.0 (32.3, 83.7)
Patients with Events,[a] n (%)	7/26 (26.9)	37/155 (23.9)	3/9 (33.3)
Recurrence of LG disease	5/26 (19.2)	27/155 (17.4)	3/9 (33.3)
Progression	0	7/155 (4.5)	0
Death	2/26 (7.7)	3/155 (1.9)	0
Probability of Remaining Event-free at 24-months, % (95% CI)[b]	67.4 (43.2, 83.1)	73.7 (64.6, 80.8)	66.7 (28.2, 87.8)
Median Duration of Follow-up, months (95% CI)[c]	23.3 (23.0, 23.9)	23.7 (23.7, 23.9)	23.9 (23.7, NE)

CI, confidence interval; CR, complete response; CRR, complete response rate; EORTC, European Organisation for Research and Treatment of Cancer; LG, low grade; KM, Kaplan–Meier; NE, not estimable.

[a]24 months after 3-month CR. Percentage is based on the number of subjects with CR at Month 3.

[b]Calculated using the KM method, with Brookmeyer–Crowley CIs.

[c]Estimated using reverse KM method.

Please refer to the Full Prescribing Information for ZUSDURI here.

ZUSDURI IMPORTANT SAFETY INFORMATION:

Contraindications

ZUSDURI is contraindicated in patients with perforation of the bladder or in patients with prior hypersensitivity reactions to mitomycin or any component of the product.

Warnings and Precautions

Risks in Patients with Perforated Bladder

ZUSDURI may lead to systemic exposure to mitomycin and severe adverse reactions if administered to patients with a perforated bladder or to those in whom the integrity of the bladder mucosa has been compromised. Evaluate the bladder before the intravesical instillation of ZUSDURI and do not administer to patients with a perforated bladder or mucosal compromise until bladder integrity has been restored.

Embryo-Fetal Toxicity

Based on findings in animals and mechanism of action, ZUSDURI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with ZUSDURI and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with ZUSDURI and for 3 months following the last dose.

Adverse Reactions

Common Adverse Reactions

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The most common (≥10%) adverse reactions, including laboratory abnormalities, that occurred in patients treated with ZUSDURI were increased creatinine, increased potassium, dysuria, decreased hemoglobin, increased aspartate aminotransferase, increased alanine aminotransferase, increased eosinophils, decreased lymphocytes, urinary tract infection, decreased neutrophils, and hematuria.

Additional Adverse Reactions Information

Clinically relevant adverse reactions occurring in <10% of patients who received ZUSDURI included increased urinary frequency, fatigue, urinary incontinence, urinary retention, urethral stenosis, genital pain, urinary urgency, genital edema, genital pruritus, genital rash, urethritis, acute kidney injury, balanoposthitis, and nocturia.

Use in Specific Populations

Lactation

Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with ZUSDURI and for 1 week following the last dose.

Preparation and Administration Information

ZUSDURI is to be administered by intravesical instillation only. Do not administer ZUSDURI by pyelocalyceal instillation or by any other route.

ZUSDURI must be prepared and administered by a healthcare provider. To ensure proper dosing, it is important to follow the preparation instructions found in the ZUSDURI Instructions for Pharmacy and administration instructions found in the ZUSDURI Instructions for Administration.

ZUSDURI may discolor urine to a violet to blue color following the instillation procedure. Advise patients for at least 24 hours post-instillation to avoid urine contact with skin, to void urine sitting on a toilet, and to flush the toilet several times after use. Advise patients to wash hands, perineum or glans with soap and water after each instillation procedure.

ZUSDURI is a hazardous drug. Follow applicable special handling and disposal procedures.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit http://www.fda.gov/medwatch or call 1-800-FDA-1088. You may also report side effects to UroGen Pharma at 1-855-987-6436.

Please see accompanying Full Prescribing Information, Instructions for Pharmacy and Instructions for Administration.

References:

1. ZUSDURI™ (mitomycin) for intravesical solution. Prescribing Information. UroGen Pharma; 2025.
2. ZUSDURI™ (mitomycin) for intravesical solution. Instructions for Pharmacy (IFP)
3. ZUSDURI™ (mitomycin) for intravesical solution. Instructions for Administration (IFA)
4. Prasad SM, Shishkov D, Mihaylov NV, et al. Primary chemoablation of recurrent low-grade intermediate-risk nonmuscle-invasive bladder cancer with UGN-102: A single-arm, open-label phase 3 trial (ENVISION). *J Urol.* 2025;213(2):205-16.
5. Prasad SM, Huang WC, Louie MJ, et al. UGN-102 achieves durable responses across EORTC recurrence score groups in adults with recurrent low-grade intermediate-risk NMIBC (ENVISION Trial). Poster presented at: ASCO-GU; Feb 27; San Francisco, CA.
6. Data on file. UroGen Pharma.