Medical Information Request: ZUSDURI™ (mitomycin) for intravesical solution and Intent to Treat (ITT) population of the Phase 3 ENVISION Trial

Thank you for your question regarding the ITT population of 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 a 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 received 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).
- 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.
- The planned duration of the study is 63 months. During the Follow-up Period, patients will return to the clinic every 3 months for up to 24 months (ie, 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 36 months (ie, 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 were included in the trial if they had recurrent LG-IR-NMIBC (Ta) with a history of LG-NMIBC requiring transurethral resection of the bladder (TURBT). Note: This refers to a previous episode(s) and not the current episode for which the patient is being screened.

Results:
Primary Endpoint:
- Complete Response (CR) at 3 months was achieved in 79.6% (95% CI: 73.9, 84.5) of patients.

Key Secondary Endpoint:
- Duration of Response (DOR)
  - For patients with a CR at 3 months, the estimated probability of remaining in CR after an additional 12 months was 82.3% (95% CI: 75.9, 87.1) as determined by Kaplan Meier analysis.
  - The median follow up was 13.9 months, and the median DOR was not estimable due to high number of patients remaining in complete response.

Other Secondary Endpoints:
- Durable Complete Response (DCR)
  - DCR was defined as the observed percentage of patients who had maintained CR 12 months after achieving CR at 3 months.

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- For patients with a CR at 3 months, the observed CR after an additional 12 months was 76.4% (95% CI 69.8 – 82.3).

Another measure of clinical interest involves the proportion of patients who are in response at various timepoints:

- The ITT population is defined as all patients having received at least 1 instillation of ZUSDURI (n = 240).
- Among all 240 patients enrolled in the Phase 3 ENVISION trial (or the ITT population), the proportion of patients who were in response at Month 15 (12 Months post 3-Month CR) was 60.8% (95% CI; 54.3, 67.0).

Exact CI's of CRR using N=240 (ITT) as the denominator

	n/N	% (95% CI)
Month 3	191/240	79.6 (73.9, 84.5)
Month 6 (3 months post 3-Month CR)	174/240	72.5 (66.4, 78.0)
Month 9 (6 months post 3-Month CR)	167/240	69.6 (63.3, 75.3)
Month 12 (9 months post 3-Month CR)	153/240	63.8 (57.3, 69.8)
Month 15 (12 months post 3-Month CR)	146/240	60.8 (54.3, 67.0)

Safety:

- 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.

	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)

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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

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.

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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. Data on file. UroGen Pharma.

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