Medical Information Request: ZUSDURI™ (mitomycin) for intravesical solution and ATLAS

Thank you for your question regarding the ATLAS trial (NCT04688931) - A Phase 3, Randomized, Controlled, Open-Label Study of the Efficacy, Durability, and Safety of ZUSDURI With or Without TURBT in Patients with Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer (LG-IR-NMIBC).

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

Background:

ATLAS was a global, randomized, open-label Phase 3 study designed to assess the long-term efficacy and safety of ZUSDURI (mitomycin) for intravesical solution (UGN-102) with or without (±) transurethral resection of bladder tumors (TURBT) versus TURBT alone for the treatment of patients with LG-IR-NMIBC. The trial was conducted from January 12, 2021, to March 17, 2023, at 72 sites in the U.S., Europe, and Israel. After deciding to pursue an alternative Phase 3 study design for ZUSDURI, and without knowledge of the post randomization data, UroGen ceased enrollment in the ATLAS study after 282 of the planned 632 patients were randomized 1:1 to ZUSDURI ± subsequent TURBT (n=142) or TURBT monotherapy (n=140). ATLAS is published in the Journal of Urology as of August 7, 2023.

ZUSDURI (mitomycin) for intravesical solution is a drug formulation of mitomycin indicated for treatment of adult patients with recurrent LG-IR-NMIBC. Utilizing UroGen's proprietary sterile hydrogel technology, a sustained release, hydrogel-based formulation, ZUSDURI is designed to enable longer exposure of bladder tissue to mitomycin, thereby enabling the treatment of tumors by non-surgical means. 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:

- Phase 3, parallel, open label.
- Eligible patients were randomized in a 1:1 ratio (stratified by the presence of previous LG-NMIBC episodes within 1 year of the current diagnosis) to ZUSDURI with or without TURBT or TURBT alone. A total of 282 patients were enrolled in the trial and randomized to receive ZUSDURI ± TURBT (n=142) or to undergo primary TURBT (n=140).
- Patients randomized to the ZUSDURI group received 6 weekly intravesical instillations, and patients randomized to the TURBT alone group received TURBT.
- The ZUSDURI admixture for intravesical instillations contains 75 mg mitomycin in 56 mL admixture (1.33 mg/mL).
- Approximately 3 months after start of treatment, patients were evaluated for complete response (CR) based on visual assessment (cystoscopy), biopsy of remaining lesions (if applicable), and voided urine cytology. If the patient had a CR, the patient did not receive any further treatment and entered the follow-up period of the study.
- Patients in either arm with residual LG disease at 3 months were considered to have non-complete response, underwent TURBT for any remaining lesions, and then entered the follow-up period.
- During the follow-up period, patients were scheduled to return to the clinic quarterly, and patients determined to be disease-free remained on study until completion of all follow-up visits or until disease recurrence, disease progression, or death was documented. Patients determined to have had a protocol-defined recurrence or progression at any follow-up or unscheduled visit were considered to have completed the study and were released to the care of their treating physicians.
- Disease-free survival (DFS) was the primary endpoint, defined as the time from randomization until treatment failure or death from any cause.

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- Secondary endpoints included Time to Recurrence (TTR), Complete Response Rate (CRR) at 3 months, Duration of Response (DOR) up to 24 months for patients who achieved CR at 3 months, Incidence of TURBT, patient reported outcomes using the EORTC-QLQ-NMIBC24, and incidence of adverse events.

Patient Population:

Inclusion Criteria	Exclusion Criteria
1. Patient who has newly diagnosed or historic LG-NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks of Screening. 2. 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). 3. Negative voiding cytology for high grade (HG) disease within 6 weeks before Screening. 4. Has adequate organ and bone marrow function as determined by routine laboratory including • Leukocytes ≥ 3,000 cells per µL; • Absolute neutrophil count ≥ 1,500 cells 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; 5. Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min. 6. 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.	1. History of carcinoma in situ (CIS) on preliminary cystoscopy within 5 years of enrollment. 2. Received Bacillus Calmette-Guérin (BCG) treatment for urothelial carcinoma (UC) within previous 1 year. 3. History of HG papillary UC in the past 2 years. 4. Known allergy or sensitivity to mitomycin that in the Investigator's opinion cannot be readily managed. 5. Clinically significant urethral stricture that would preclude passage of a urethral catheter. 6. History of pelvic radiotherapy. 7. History of: • Neurogenic bladder; • Active urinary retention; • Any other condition that would prohibit normal voiding. 8. Past or current muscle invasive bladder cancer (ie, T2, T3, T4) or metastatic UC or concurrent upper tract UC 9. Current tumor grading of T1. 10. Concurrent upper tract urothelial carcinoma (UTUC). 11. Has an underlying substance abuse or psychiatric disorder. 12. History of prior treatment with an intravesical chemotherapeutic agent except for a single dose of chemotherapy immediately after any previous TURBT. 13. Has previously participated in a study in which they received ZUSDURI. 14. Has participated in a study with an investigational agent or device within 30 days of enrollment.

Results:

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A total of 282 patients were enrolled in the trial and randomized to receive ZUSDURI ± TURBT (n=142) or to undergo primary TURBT (n=140). The median age was 68 years in the ZUSDURI arm and 67 years in the TURBT arm. Most participants were male in both study arms. Fifty-four patients (38%) in the ZUSDURI arm and 65 patients (46%) in the TURBT arm had prior history of LG-NMIBC. Fifty-two patients (37%) in the ZUSDURI arm and 64 patients (46%) in the surgery arm had prior TURBT. At baseline, multifocal tumors were identified in 82 patients (58%) in the ZUSDURI arm and 94 in TURBT arm (67%) and 67 (47%) ZUSDURI patients and 59 (42%) surgery patients had tumors > 3 cm.

At the first disease assessment 3 months after start of treatment, CR was achieved by 92 ZUSDURI patients (65% [95% CI: 56.3, 72.6]) and 89 TURBT patients (64% [95% CI: 55.0, 71.5]). DFS at 15 months after randomization was estimated to be 72% for patients in the ZUSDURI ± TURBT arm and 50% for patients in the TURBT monotherapy arm by Kaplan-Meier analysis (HR – 0.45). Estimated DOR at 12 months was 80% after induction treatment with ZUSDURI and 68% after primary TURBT amongst patients achieving CR at the 3-month assessment (HR – 0.46). In a post hoc sensitivity analysis that excluded residual LG disease as DFS events at the 3-month assessment in the TURBT alone arm, estimates of DFS remained favorable for the ZUSDURI ± TURBT group (HR = 0.59 [95% CI: 0.38, 0.91]).

Safety Outcomes

A total of 138 patients who received ≥1 dose of ZUSDURI in the primary chemoablation treatment arm and 132 patients who were treated by primary TURBT represented the safety analysis population. Treatment-emergent adverse events (TEAEs) occurred more commonly in patients treated with ZUSDURI (75%) compared to 48% in the TURBT monotherapy arm. TEAEs related to the study treatment were experienced by 54 (39%) patients in the ZUSDURI ± TURBT arm vs 15 (11%) in the TURBT alone arm. However, patients in the primary chemoablation treatment arm were queried weekly during induction therapy regarding adverse effects associated with treatment, whereas patients in the surgical arm were evaluated at monthly intervals via telephone contact up to the 3-month visit. This may have introduced an ascertainment bias into the study due to imbalance in evaluations which in turn may have led to underestimation of TEAEs associated with TURBT. Treatment discontinuation and study discontinuation due to adverse events occurred in 5 (3.6%) and 4 (2.9%) patients receiving ZUSDURI. Serious TEAEs occurred in 12 patients (8.7%) who received ZUSDURI and 7 patients (5.3%) in the TURBT arm. However, no serious TEAEs in the ZUSDURI group and one in the TURBT monotherapy group (postoperative hematuria) were considered by the investigator to be related to treatment. The most commonly reported adverse events (>5%) in the ZUSDURI ± TURBT arm of the study were dysuria (30%), micturition urgency (18%), nocturia (18%), and pollakiuria (16%). One death occurred during the study in the TURBT arm which was attributed to infection with COVID-19.

Patient Reported Outcomes (PRO)

Treatment effects on disease-related symptoms, functioning, and health-related quality of life were assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire for Non-muscle Invasive Bladder Cancer patients (EORTC-QLQ-NMIBC24). The measures reported for change from baseline were either improved or not worsened in those treated with ZUSDURI ± TURBT or TURBT alone in the ATLAS trial.

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.

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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.

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.

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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, Huang WC, Shore ND, Hu B, Bjurlin M, Brown G, Genov P, Shishkov D, Khuskivadze A, Ganev T, Marchev D, Orlov I, Kopyltsov E, Zubarev V, Nosov A, Komlev D, Burger B, Raju S, Meads A, Schoenberg M. Treatment of Low-Grade Intermediate-Risk Nonmuscle-Invasive Bladder Cancer with UGN-102 ± Transurethral Resection of Bladder Tumor (TURBT) Compared to TURBT Monotherapy: A Randomized, Controlled, Phase 3 Trial (ATLAS). J Urol. 2023 Aug 7: Epub ahead of print. PMID: 37548555.
5. Data on file. UroGen Pharma.

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