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

Thank you for your question regarding the Phase 2b OPTIMA II trial (NCT03558503) - Primary Chemoablation of Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer (LG-IR-NMIBC) Using ZUSDURI, a mitomycin-containing reverse thermal gel.

ZUSDURI™ is indicated for the treatment of adult patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC).[1]

Background:
The Phase 2b OPTIMA II trial (OPTimized Instillation of Mitomycin for Bladder Cancer Treatment) was an open-label, single-arm trial designed to assess the efficacy and safety of ZUSDURI (UGN-102), a mitomycin-containing reverse thermal gel, as a non-surgical alternative to treating recurrent LG-IR-NMIBC. The trial was conducted from October 15, 2018 to October 21, 2020 at 20 sites in the United States and Israel. Eighty (80) patients were screened for eligibility, and sixty-three (63) were ultimately enrolled in the study and treated, representing the intent to treat analysis set.

ZUSDURI (mitomycin) for intravesical solution is a drug formulation of mitomycin developed for the treatment of adult patients with recurrent LG-IR-NMIBC. 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:
- Phase 2b, single arm, open label.
- Eligible patients received 6 once-weekly intravesical instillations of ZUSDURI.
- The ZUSDURI admixture administered in the trial contains 75 mg mitomycin in 56 mL sterile hydrogel (1.33 mg/mL).
- Treatment could be postponed for up to 4 weeks in the event of a potential safety concern (urinary tract infection, inadequate organ function).
- The ablative effect of ZUSDURI was evaluated at the 3-month visit, which occurred 4 to 6 weeks after the last weekly instillation and 3 months after treatment initiation.
- Response to treatment was determined based on visual assessment (cystoscopy), biopsy of remaining lesions (if applicable), and voided urine cytology.
- If cystoscopy indicated no remaining tumors and urine cytology was negative, the patient had no detectable disease and was considered to have had a complete response (CR).
- If the bladder was free of tumor endoscopically but cytology was positive, the investigators were required to exclude UTUC and occult carcinoma of the bladder or urethra. However, even if UTUC was confirmed, the patient was still considered to have had a CR.
- If any lesions were detected, even if they appeared necrotic, a biopsy was taken from the suspect tissue. If the biopsy was negative for cancer, the case was considered CR, and if the biopsy was positive, the case was considered non-CR.
- Patients who achieved CR continued to have monthly telephone contacts to document any adverse events (AEs) and were assessed for evidence of disease recurrence at 6, 9 and 12 months after the first instillation of ZUSDURI.
- Patients considered non-CR discontinued the study and were treated with standard of care therapy as determined by their treating physicians.
- The primary efficacy endpoint was CR rate, defined as the percentage of patients with CR at the 3-month visit.

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- The secondary efficacy endpoint was durability of CR in patients who achieved CR at the 3-month visit, defined as the percentage of patients with no detectable disease at 6, 9 and 12 months after treatment initiation. Duration of CR was defined as time from the date of evidence of CR at the 3-month visit to the earliest date of recurrence.
- Additionally, changes in patient reported side effects from baseline to the primary endpoint of 3 months, and patient interviews about tolerability and patient experience was a secondary endpoint.
- Patients who remained in CR at 12 months were eligible to enroll in a 4-year long-term follow-up study. Patients' disease status was assessed semiannually until disease recurrence, progression, or death.

Patient Population:

Inclusion Criteria	Exclusion Criteria
1. Eligible patients were ≥ 18 years of age and willing and able to sign an informed consent and comply with the protocol. 2. Had newly diagnosed or historic LG-NMIBC (Ta) histologically confirmed by cold cup biopsy at screening or within 6 weeks of screening (with visible tumor left in situ). 3. Negative voiding cytology for high-grade (HG) disease within 6 weeks before screening 4. IR disease was defined as having 1 or 2 of the following: • presence of multiple tumors, • solitary tumor >3 cm, • recurrence (1 or more occurrence of LG-NMIBC within 1 year of the current diagnosis) 5. Adequate organ and bone marrow function as determined by routine laboratory testing: • 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 ≤ 2.5 × ULN; • Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min. 6. Had no evidence of active urinary tract infection (UTI) at Screening and Baseline visits.	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 2 years. 3. History of HG papillary UC in the past 2 years. 4. Known allergy or sensitivity to mitomycin. 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 (ie, T2, T3, T4) or metastatic UC or concurrent upper tract urothelial carcinoma (UTUC). 9. Had participated in a study with an investigational agent or device within 30 days of enrollment. 10. History of prior treatment with an intravesical chemotherapeutic agent with the exception of a single dose of chemotherapy immediately after any previous transurethral resection of bladder tumors (TURBT). 11. Had 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.

Results:

A total of 63 patients were enrolled in OPTIMA II and treated with one or more instillations of ZUSDURI, representing the intent to treat analysis set (Figure 1). At baseline, 49 patients (78%) had recurrent LG-NMIBC and of those patients, 28 (44%) had a previous episode within 1 year of the current diagnosis. 37 of 49 patients (76%) had 2 prior TURBTs and 28 of 49 patients (57%) had 3 prior TURBTs. Of all those enrolled, 57 (90%) completed 6

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instillations of ZUSDURI according to protocol. Six patients discontinued treatment due to AE. Duration of CR was estimated using the Kaplan-Meier method. If a patient did not have a recurrence, the patient was censored at the date of the last adequate disease assessment or date of death.

Forty-one (41) patients (65%) achieved CR at 3 months after treatment initiation (95% CI 52.0, 76.7). Among 22 patients who were non-CR, 20 showed evidence of persistence or worsening of disease and 2 were indeterminate. Of the 41 patients with CR at 3 months, 39 (95%) were disease free at 6 months, 30 (73%) were disease free at 9 months, and 25 (61%) remained disease free 12 months after treatment initiation. Thirteen patients (32%) had disease recurrence (2 of whom were determined to have a more aggressive tumor than diagnosed at screening – this was considered evidence of disease progression). Three patients terminated their study involvement early: 1 due to an AE, 1 due to death, and 1 patient due to concerns related to COVID-19.

The median duration of CR was not estimable. However, the probability of durable response 9 months after CR (12 months after treatment initiation) estimated by the Kaplan-Meier method was 72.5% (95% CI 54.4, 84.3) (Figure 2).

Final results from the phase 2b OPTIMA II trial were reported in November 2020 and published in the Journal of Urology.[4]

Safety Outcomes

Overall, 57 of 63 patients (90%) experienced treatment emergent adverse events (TEAE). Of those patients who experienced TEAEs, 40 (63%) were considered related to study drug or procedure. Five patients (8%) had 1 serious TEAE, none of which was considered to be related to the study drug or procedure. The most frequently reported TEAEs were dysuria in 26 of 63 patients (41%), urinary frequency in 13 (21%), hematuria in 10 (16%), micturition urgency and UTI in 9 patients (14%), and fatigue in 7 patients (11%). Regarding TEAEs of special interest (lower urinary tract symptoms, allergic reactions, voiding interruption due to urethral/penile edema, genitourinary infections, inadvertent or accidental exposure to ZUSDURI and bone marrow suppression), 43 of 44 patients (98%) had events that were mild or moderate in severity and 35 of 44 (80%) had events that resolved during the study. Among the 9 cases with TEAEs of special interest mentioned previously that did not resolve, 6 events were considered not related to study drug or procedure.

Results from 4-year long-term follow-up (LTFU):

Among the 41 patients who achieved a CR at 3 months, 25 remained in CR at 12 months after treatment initiation, and entered 4-year, long term follow-up. The median Kaplan–Meier estimate of DoR was 24.2 months (95% CI 9.7, 47.2), with a median follow-up time of 33.6 months (95% CI 10.8, 42.9). Twenty patients (48.8%) experienced recurrence of low-grade disease, 1 patient progressed to high-grade disease, and 1 patient died due to a cardiac disorder. Five patients (20%) remained disease free at the time of the 4-year long term follow-up data analysis. A limitation of this study was the small sample size in the long term follow up group. In addition, no safety or quality of life data were collected in the extension phase of the study (12-48 months).

	ZUSDURI
CR at 3 Months, n (%)	41/63 (65.1)
Patients With Events Between 3 and 12 Months, n (%)	22/41 (53.7)
Recurrence of LG disease	20 (48.8)
Progression to HG disease	1/41 (2.4)

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Death	1/41 (2.4)
Patients Censored, n (%)	19/41 (46.3)
Early discontinuation in parent study CR at end of parent study, did not enter LTFU Early discontinuation in rollover study Ongoing CR in rollover study	2/41 (4.9) 8/41 (19.5) 4/41 (9.8) 5/41 (12.2)
Continued in LTFU, n (%)	25/41 (61.0)
Early discontinuation in LTFU	4/25 (16.0)
Ongoing CR	5/25 (20.0)
Median follow-up time, months (95% CI) for all 41 LTFU patients	33.61 (10.8, 42.9)
KM estimate of median DoR, months (95% CI), **all 41 LTFU patients**	24.2 (9.7, 47.2)

CR-Complete response; LG-Low-grade; HG-High-grade; LTFU-Long-term follow-up; KM-Kaplan-Meier; DoR-Duration of response

Patient Reported Outcomes (PRO)

Stover et al. published the first study reporting on patient-reported side effects of ZUSDURI.[5] Patient-reported symptoms, functioning, and quality-of-life were measured by changes from baseline in the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire for non-muscle invasive bladder cancer (QLQ-NMIBC24) or EORTC-QLQ-NMIBC24. Of the 63 patients enrolled in OPTIMA II, 44 were in a cohort completing the quarterly PRO measure assessing side effects. 10 of 44 patients (23%) were interviewed after the trial to understand tolerability for future patients making treatment decisions.

Figures

Figure 1: Flow Diagram

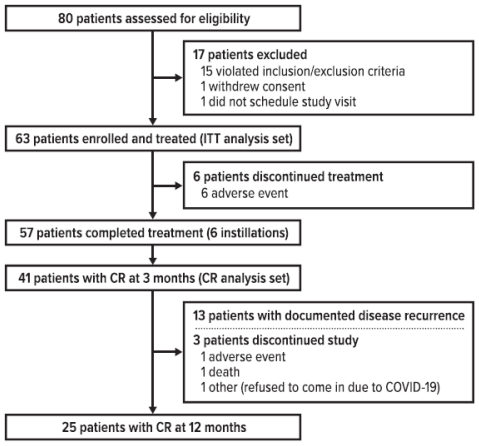

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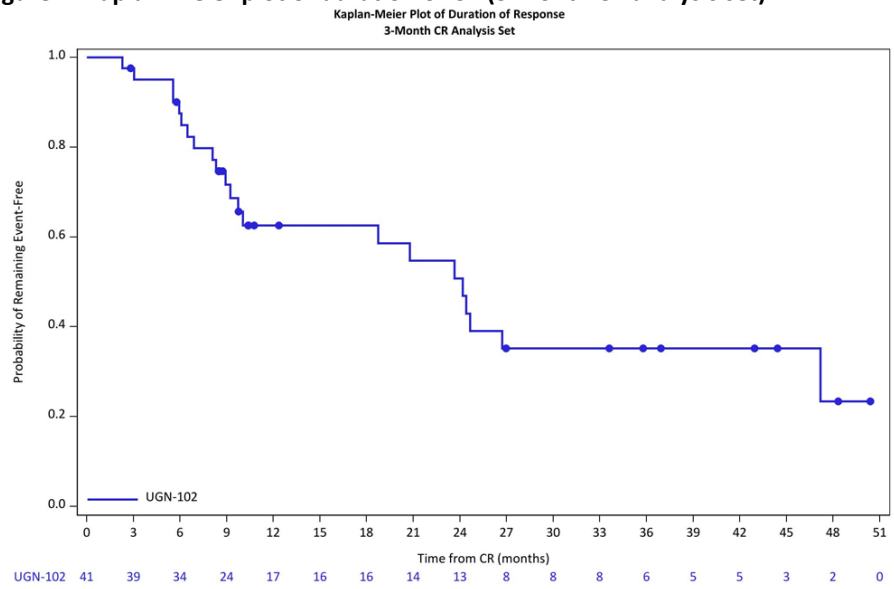
Figure 2: Kaplan-Meier plot of duration of CR (3-month CR analysis set)



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

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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. Chevli KK, Shore ND, Trainer A, et al. Primary chemoablation of low-grade intermediate-risk nonmuscle-invasive bladder cancer using UGN-102, a mitomycin-containing reverse thermal gel (OPTIMA II): A phase 2B, open-label, single-arm trial. Journal of Urology. 2022;207(1):61-69.
5. Stover AM, Basak R, Mueller D, Lipman R, Teal R, Hilton A, Giannone K, Waheed M, Smith AB. Minimal Patient-Reported Side Effects for a Chemoablative Gel (UGN-102) Used as Frontline Treatment in Adults with Nonmuscle-Invasive Bladder Cancer. J Urol. 2022 Sep;208(3):580-588. doi: 10.1097/JU.0000000000002747. Epub 2022 May 31. PMID: 35640276.
6. Data on file. UroGen Pharma.