Medical Information Request: Patient Report Outcomes (PROs) for ZUSDURI™ (mitomycin) for intravesical solution and OPTIMA II, ATLAS, and ENVISION trials

Thank you for your question regarding patient reported outcomes for ZUSDURI.

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

Utilizing UroGen's proprietary sterile hydrogel technology, ZUSDURI (UGN-102) 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.

The information provided in this document is limited to the assessment of patient-reported outcomes.

Background:

OPTIMA II **(NCT03558503)** was an open-label, single-arm, Phase 2B 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 low-grade intermediate-risk non-muscle invasive bladder cancer (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.

ATLAS **(NCT04688931)** 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 Sponsor discussions with the FDA, patient accrual in ATLAS was suspended at 282 participants (45% of planned) without knowledge of the data. The trial continued until all ongoing patients had completed at least 12 months of follow-up after the 3-month Visit. ATLAS is a supportive study with secondary endpoints that provide a randomized comparison of ZUSDURI to community-based care for LG-IR-NMIBC (TURBT) and facilitate the assessment of consistency of ZUSDURI efficacy results (CRR, DOR, and DCR) across the development program.

ENVISION **(NCT05243550)** was 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.

PRO assessments of patients treated with ZUSDURI were conducted and analyzed for all three trials, OPTIMA II, ATLAS, and ENVISION.

Methods:

In all three trials, ZUSDURI was administered as 6 once weekly intravesical instillations, followed by a 3-month disease assessment for complete response (CR). Patients who achieved a CR were eligible for study follow-up.

The European Organisation for Research and Treatment of Cancer (EORTC) NMIBC-specific Quality of Life Questionnaire (QLQ-NMIBC24) was administered to patients as a secondary endpoint in ATLAS and exploratory endpoint in OPTIMA II and ENVISION. Additionally, the EORTC Core Quality of Life Questionnaire for Cancer Patients (QLQ-C30) was administered to patients as an exploratory endpoint in ENVISION.

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Mean baseline PRO scores and changes from baseline (CFB) were calculated for each trial. Scores for each scale ranged from 1 (not at all) to 4 (very much), transformed to a 0–100 scale, with a high score for a symptom scale/item representing a high level of symptomatology/problems. Descriptive statistics were used to describe baseline and change from baseline scores; a positive change from baseline indicates worsening in symptom. Minimal clinically important differences (MCIDs) were used to identify clinically meaningful CFB. As lower urinary symptoms were the most commonly reported treatment-emergent adverse events (TEAEs) in ZUSDURI clinical trials, a secondary aim of the analysis was to assess associations between QLQ-NMIBC24 urinary symptom scores and clinically reported urinary TEAEs with ZUSDURI in ATLAS and ENVISION.

OPTIMA II:

- QLQ-NMIBC24 was administered at Day 1 of treatment (baseline), at the 3-month visit, and every 3 months during the follow-up period starting at the 6-month visit until 12 months. QLQ-NMIBC24 was not administered during the treatment period (Weeks 2-6).
- Baseline data was not collected on all patients as the PRO assessment was added as a protocol amendment.
- Delayed or missed visits beyond the 3-month visit caused by the COVID-19 pandemic precluded the calculation of CFB for some patients at some timepoints.
- During the follow-up period, the QLQ-NMIBC24 was only administered to patients who achieved a CR at the 3-month visit.

ATLAS:

- QLQ-NMIBC24 was administered during the screening period (baseline), at each treatment visit during the ZUSDURI treatment period (Weeks 1-6; assessments reported for Weeks 2-6 herein), at the 3-month visit, and every 3 months during the follow-up period starting at the 6-month follow-up visit until completion of all follow-up visits or documented recurrence, progression, or death.
- During the follow-up period, the QLQ-NMIBC24 was administered to all patients regardless of CR or non-CR at the 3-month visit.
- A post-hoc analysis was conducted to summarize the PRO data among the subgroup of patients with a CR at the 3-month visit in ATLAS.

ENVISION

- QLQ-NMIBC24 and QLQ-C30 were administered at Day 1 of treatment (baseline), at each treatment visit during the treatment period (Weeks 2-6), at the 3-month visit, every 3 months during the follow-up period starting at the 6-month follow-up visit and up to the 27-month visit, and every 6 months thereafter until documented recurrence, progression, or death.
- During the follow-up period, the PRO assessments were only administered to patients who achieved a CR at the 3-month visit.

PRO assessment schedule in OPTIMA II, ATLAS, and ENVISION

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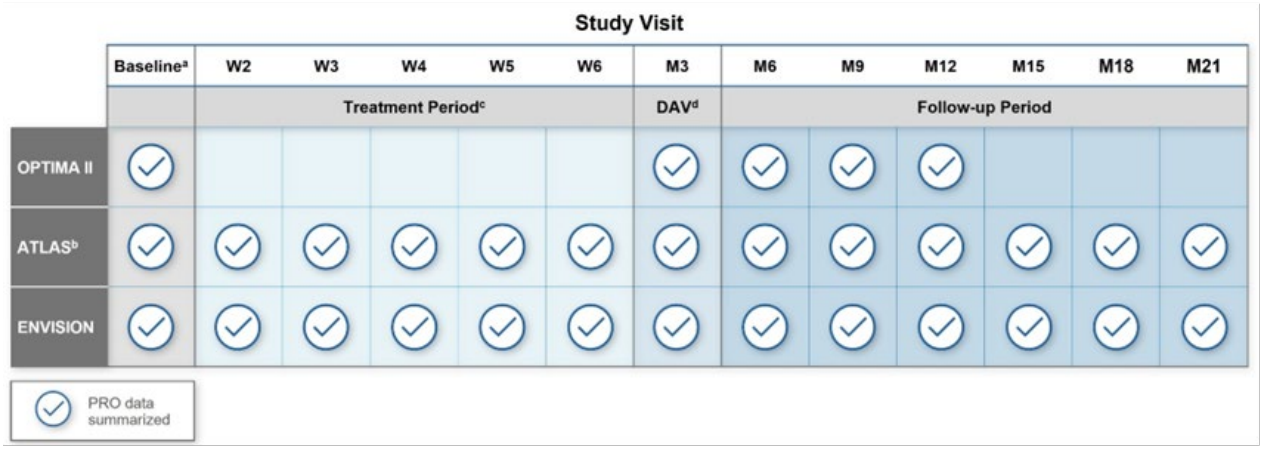

Patient Population(s):
PRO assessments were completed in the intent-to-treat (ITT) populations of OPTIMA II and ENVISION, and in the safety analysis population of ATLAS.

In OPTIMA II, ENVISION, and ATLAS trials:

- Patients were age ≥ 18 years with LG-IR-NMIBC (Ta) diagnosed using cold cup biopsy (with visible tumor left in situ) and negative voiding cytology for high-grade (HG) disease
- Intermediate risk (IR) disease was defined as having 1 or 2 of the following: Presence of multiple tumors, solitary tumor >3 cm, and/or recurrence of LG-NMIBC within 1 year of the current diagnosis

In the OPTIMA II study (single-arm, N=63), patients were included if they had newly diagnosed or recurrent LG-IR-NMIBC.

In the ENVISION study (single-arm, N = 240), 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 to the current episode for which the patient is being screened.

In the ATLAS study (N = 282), patients with newly diagnosed or recurrent LG-IR-NMIBC were randomized to intravesical ZUSDURI (n=142) or TURBT (n=140).

Results:
PRO completion rate for ATLAS was 90% and ENVISION was 94.1%. Mean baseline PRO scores were mostly indicative of low patient-perceived symptom burden and high level of functioning and QoL. Treatment with ZUSDURI **did not result** in sustained decrements to functioning and symptom burden. Previous work identified minimal clinically important differences (MCIDs), and none of the measured domains reached the worsening MCID threshold at 3 or 12 months indicating the treatment period **did not negatively affect QoL.**

QLQ-NMIBC24 (OPTIMA II, ATLAS, ENVISION)
Baseline QLQ-NMIBC24 scores in each trial were indicative of low patient-perceived symptom burden and moderate impact of NMIBC on functioning.
Functional Scales/Items:

- In ATLAS and ENVISION, mean scores for each QLQ-NMIBC24 scale/item were generally stable and similar to baseline during the ZUSDURI treatment period (Weeks 2-6). *PROs were not assessed for the treatment period in OPTIMA II.*
- No clinically meaningful change from baseline (CFB) in sexual function were observed across the trials.

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- In ATLAS, there were clinically meaningful deteriorations from baseline in sexual enjoyment at Week 5 (mean [SD] CFB: 12.1 [30.4]; MCID: 11.64) and Month 18 (mean [SD] CFB: 16.7 [34.4]).
- In ENVISION, there was a clinically meaningful deterioration from baseline in sexual enjoyment at Month 21 (mean [SD] CFB: 13.3 [18.3]).
- In OPTIMA II, no clinically meaningful CFB in sexual enjoyment were observed. In ENVISION, clinically meaningful CFB was observed at Month 21 [mean [SD] CFB: 13.3 (18.3)]

Symptom Scales/Items:

- No clinically meaningful mean CFB in urinary symptom scores were observed at any time point in OPTIMA II or ENVISION. In ATLAS, there was a clinically meaningful improvement from baseline in urinary symptom score starting at Month 3 after initiation of ZUSDURI treatment (mean [SD] CFB: -10.7 [17.9]; MCID: 6.57), which was maintained throughout the rest of the follow-up period.
  In ATLAS, clinically meaningful improvements from baseline were observed at Month 3 for malaise (mean [SD] CFB: -4.4 [13.6]; MCID: 4.37), future worries (mean [SD] CFB: -12.7 [26.5]; MCID: 11.08), and bloating and flatulence (mean [SD] CFB: -7.7 [18.0]; MCID: 7.59).
- In OPTIMA II, clinically meaningful improvements from baseline in future worries were observed at Months 6 and 9 (mean [SD] CFB: -11.7 [24.6] and -13.8 [26.9], respectively).
- In OPTIMA II, there was a clinically meaningful worsening from baseline in sexual intimacy score at Month 3 (mean [SD] CFB: 14.8 [24.2] based on 9 patients; MCID: 8.69) and in male sexual problems at Month 9 (mean [SD] CFB: 19.4 [38.8]; MCID: 15.3).
- No clinically meaningful CFB were observed for the intravesical treatment issues or perceived risk of contaminating partner scales/items at any time point across trials
- No clinically meaningful worsening of QLQ-NMIBC24 symptom scores based on MCID thresholds was observed at any time point in ATLAS.

ATLAS 3-Month CR Subgroup Analysis (N=92):

- QLQ-NMIBC24 findings were similar to the safety analysis population used for the full PRO assessment.
- Clinically meaningful improvements from baseline were observed at Weeks 2-3 and Month 3 and onward for urinary symptoms, at Month 3 and onward for bloating and flatulence, and at several time points during the follow-up period for malaise.

QLQ-C30 (ENVISION)

- Mean baseline scores were high for global QoL and functioning scales and low across symptom scales, indicating a high level of functioning and QoL and a low symptom burden in the study population.
- The mean (SD) baseline global QoL score was 74.6 (18.0) and mean (SD) CFB ranged from -2.2 (15.4) at Week 6 to 4.5 (14.8) at Month 21.
- Mean changes did not reach the MCID threshold of a 10-point change for any scales/items at any point during or after treatment with ZUSDURI.

QLQ-NMIBC24 Urinary Symptoms by Occurrence of Urinary TEAEs (Secondary aim)

ATLAS

- There were no clinically meaningful changes from baseline in urinary symptom scores during the ZUSDURI treatment period for patients who experienced a urinary TEAE.
- Patients who did not experience a urinary TEAE had clinically meaningful improvements from baseline starting at Week 2.
- From Month 3 and onwards, clinically meaningful improvements from baseline were observed regardless of urinary TEAE occurrence.

ENVISION

- Patients who experienced a urinary TEAE with ZUSDURI had a clinically meaningful worsening of urinary symptom score at Weeks 5 and 6 (mean [SD] CFB: 10.1 [16.6] and 11.2 [17.7], respectively). This observation was transient, as the change from baseline decreased below the MCID threshold by Month 3 and mean scores were similar to baseline thereafter.

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- Patients who did not experience a urinary TEAE with ZUSDURI treatment did not have any clinically meaningful changes in urinary symptom scores, with mean scores remaining near baseline throughout the treatment and follow-up periods.

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

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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. Prasad SM, Huang WC, Shore ND, et al. Treatment of low-grade intermediate-risk nonmuscle-invasive bladder cancer with UGN-102 ± transurethral resection of bladder tumor compared to transurethral resection of bladder tumor monotherapy: A randomized, controlled, phase 3 trial (ATLAS). J Urol. 2023;210(4):619–629.
6. 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.
7. Data on file. UroGen Pharma.

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