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Oncologic Drugs Advisory Committee (ODAC) Meeting

May 21, 2025

NDA 215793

Drug name: UGN-102 (mitomycin) for intravesical solution

Applicant: UroGen Pharma Ltd.

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug UGN-102 (mitomycin) for intravesical solution (NDA 215793) to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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# Glossary

| Abbreviation or Special Term | Definition |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BCG | Bacillus Calmette-Guérin |
| BL005 | OPTIMA II study |
| BL006 | ATLAS study |
| BL010 | Small home instillation study |
| BL011 | ENVISION study |
| CFB | Change from baseline |
| CI | Confidence interval |
| CIS | Carcinoma in situ |
| $C_{max}$ | Maximum plasma concentration |
| CMC | Chemistry, manufacturing, and controls |
| CR | Complete response |
| CRR | Complete response rate |
| CSR | Clinical study report |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCO | Data cutoff |
| DCR | Durable complete response |
| DFS | Disease-free survival |
| DOR | Duration of response |
| eCRF | Electronic case report form |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EoS | End of study |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | Gamma glutamyl transferase |
| HG | High-grade |
| HR | Hazard ratio |
| ICH | International Council for Harmonization |
| IND | Investigational New Drug |
| IR | Intermediate-risk |
| ISE | Integrated Summary of Effectiveness |
| ITT | Intent-to-treat |
| IVCT | Intravesical chemotherapy |
| IVT | Intravesical therapy |
| KM | Kaplan-Meier |
| LG | Low-grade |
| LG-IR-NMIBC | Low-grade intermediate-risk non-muscle invasive bladder cancer |
| LG-UTUC | Low-grade upper tract urothelial carcinoma |
| LUTS | Lower urinary tract symptoms |
| MCID | Minimal clinically important difference |
| MIBC | Muscle invasive bladder cancer |
| NCR | Non-complete response |
| NDA | New Drug Application |

| Abbreviation or Special Term | Definition |
|---|---|
| NMIBC | Non-muscle invasive bladder cancer |
| NR | Not reported |
| ODAC | Oncologic Drugs Advisory Committee |
| POC | Proof of concept |
| PRO | Patient-reported outcome |
| PT | Preferred term |
| QLQ-C30 | Quality of Life Questionnaire for Cancer Patients |
| QLQ-NMIBC-24 | Quality of Life Questionnaire for Non-muscle Invasive Bladder Cancer |
| QoL | Quality of life |
| SAE | Serious adverse event |
| SD | Standard deviation |
| SEER | Surveillance, Epidemiology, and End Results |
| SOC | System organ class |
| SoC | Standard of care |
| TEAE | Treatment-emergent adverse event |
| TURBT | Transurethral resection of bladder tumor |
| US | United States |
| UTUC | Upper tract urothelial carcinoma |

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# 1 Introduction

## 1.1 Proposed Indication(s)

A 505(b)(2) application has been submitted for UGN-102 (mitomycin) for intravesical solution. The proposed indication is for the treatment of adult patients with recurrent low-grade intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC). The recommended dose of UGN-102 is 75 mg (56 mL) instilled once weekly for 6 weeks into the bladder via a urinary catheter. UGN-102 is for intravesical instillation only, not for intravenous, topical or pyelocalyceal use, or for oral administration.

## 1.2 Purpose of the Meeting

**FDA's Summary of the Purpose of the Meeting:**

The Applicant has submitted a New Drug Application (NDA) for their investigational product UGN-102, which is an intravesically administered mitomycin formulation intended for use in patients with low-grade, intermediate-risk non-muscle invasive bladder cancer (LG-IR-NMIBC). No drugs are currently FDA-approved for the treatment of patients with LG-IR-NMIBC; this is a novel disease setting for drug development. The U.S. Food and Drug Administration (FDA) is convening the Oncologic Drugs Advisory Committee (ODAC) to discuss whether:

a. Durable complete response assessed in a single-arm trial can establish efficacy in the LG-IR-NMIBC population.
b. The overall benefit-risk of the investigational treatment is favorable.

The FDA considers the Applicant's ENVISION trial to be the primary source of evidence to support this NDA. ENVISION was a single-arm trial conducted in patients with recurrent LG-IR-NMIBC. In this disease setting, there is a wide range of recurrence probabilities that depend on several factors. Given that ENVISION lacked a concurrent control arm, the primary endpoints of complete response (CR) and duration of response (DOR) are difficult to interpret.

While CR indicates drug activity of UGN-102, it is unclear whether the observed DOR can be attributed to the investigational product or instead reflects the natural history of the disease. The lack of a concurrent control also does not allow for generation of comparative safety data to standard of care therapies in this setting, which typically includes transurethral resection of bladder tumor (TURBT) with or without a single post-operative instillation of intravesical chemotherapy. The FDA recommended a randomized trial design to the Applicant several times during their product's development due to these concerns.

As the Applicant chose not to conduct a randomized trial with a design and endpoints that the FDA considered appropriate to demonstrate substantial evidence of effectiveness for UGN-102, the FDA informed the Applicant that a large single-arm trial could potentially serve as a major trial to support approval of UGN-102. The FDA stated that such a trial would require a large

sample size and sufficient duration of follow-up to evaluate whether the therapy demonstrated a clinically meaningful DOR and did not impact the safety of subsequent TURBT. The FDA further stated that demonstrating treatment effect that is distinct from the natural history of the disease would be critical, safety results would be considered, and the proposed follow up of 18 months after response may not adequately capture durability. Lastly, the FDA noted to the Applicant that an NDA supported by data generated in a single-arm trial would likely require discussion at ODAC.

# 2 Efficacy

## 2.1 Description of Clinical Setting

### 2.1.1 Overview of Low-Grade Intermediate-Risk Non-Muscle Invasive Bladder Cancer

The Applicant's Position:

An estimated 83,190 new cases of bladder cancer are diagnosed annually in the United States (US), and the estimated prevalence of bladder cancer is 730,000.[1,2] Non-muscle invasive bladder cancer (NMIBC) refers to tumors localized to the bladder's inner lining and is the most common form of bladder cancer, accounting for ~75% of cases at the time of diagnosis.[3] NMIBC is a clinically heterogeneous group of cancers with a wide range of recurrence and progression probabilities that depend on several clinical and pathologic factors.[4,5] Risk stratification systems are used to guide treatment and classify NMIBC tumors as low, intermediate, or high risk based on the risk of disease recurrence after treatment.

Intermediate-risk (IR) NMIBC is defined by the International Bladder Cancer Group as low-grade (LG) Ta (papillary) tumors that are large (>3 cm), multifocal, and/or recurrent, as well as LG T1 (invading the lamina propria) tumors.[6] Disease relapse is common, and many patients with LG-IR-NMIBC experience recurrence within a year after treatment. Although LG-IR-NMIBC has a high risk of recurrence, it has a low risk of disease progression (Section 2.1.2.2). There are approximately 60,000 patients with recurrent LG-IR-NMIBC presenting for treatment annually in the United States.[2,7,8]

In the United States, NMIBC typically affects older adults and more frequently men, with a median age at diagnosis of 73 years, according to Surveillance, Epidemiology, and End Results (SEER) data.[2,3] The US incidence of bladder cancer by race per the SEER database is 89.52% White, 5.80% Black, 0.33% American Indian/Alaska Native, and 4.36% Asian or Pacific Islander.[9]

NMIBC is more likely to affect older adults, in whom comorbidities and polypharmacy (including anticoagulants, which typically must be discontinued before surgery) are common.[3,10] A retrospective analysis of 26,045 bladder cancer survivors >65 years of age reported high comorbidity rates, including congestive heart failure (6%-19%), diabetes (23%-29%), and chronic obstructive pulmonary diseases (17%-20%).[11]

The FDA's Position: There is limited contemporary evidence to correlate low, intermediate, and high-risk categories of NMIBC with clinical outcomes. These categories are thought to broadly

estimate the likelihood of recurrence and progression. The FDA agrees with the Applicant that, based on available literature, the risk of progression in this IR-population is low. However, the risk of recurrence encompasses a wide range. In addition to heterogenous outcomes across broad risk categories, there are both heterogenous risks of recurrence within the IR category and varied definitions of IR across guidelines and studies, which makes predicting the natural history of the disease difficult. Varied practice patterns for the management of IR-NMIBC (e.g. post-TURBT with or without single dose chemotherapy, induction chemotherapy with maintenance, or BCG) may also lead to heterogenous outcomes.

### 2.1.2 Current Treatment Landscape and Unmet Need

The Applicant's Position:

#### *2.1.2.1 Diagnosis, Management, and Surveillance of Non-Muscle Invasive Bladder Cancer*

For the diagnosis of NMIBC, major guidelines recommend cystoscopy and biopsy, urine cytology, imaging of the upper urinary tract, and transurethral resection of bladder tumor (TURBT).[4,12] The management of NMIBC is guided by stratifying patients according to their risk of disease recurrence or progression based on pathological characteristics, including tumor grade, stage, and size; frequency of recurrence; and time to recurrence.[3-6,12]

TURBT is recommended by major guidelines for the initial management of LG-IR-NMIBC because it allows diagnostic staging of the tumor, together with tumor resection. However, additional TURBT may be required 2 to 6 weeks later if the primary resection is incomplete.[3,12] Clinical practice guidelines indicate that following IR-NMIBC tumor resection with TURBT, a single intravesical instillation of chemotherapy should be considered, which may reduce the risk of recurrence by up to ~20%, and that additional induction with or without maintenance chemotherapy or Bacillus Calmette-Guérin (BCG) may be administered.[12,13] However, it has been reported that few US patients (~16%) receive intravesical therapy (IVT) after TURBT because of limited additional benefit as well as logistical and financial barriers.[14-17] For surveillance of IR-NMIBC, guidelines recommend performing cystoscopies at 3- to 6-month intervals for the first 2 years, followed by less-frequent, long-term monitoring. Evidence in the literature suggests that tumor status at 3 months after TURBT is a strong predictor for recurrence at later time points and drives subsequent treatment decisions.[18,19]

While there has been innovation and new drug approvals for high-grade (HG) bladder cancer (see Table 10 in Appendix 3), there are no US Food and Drug Administration (FDA)–approved therapies for LG-IR-NMIBC. The current standard of care (SoC) of TURBT, which is usually conducted under general anesthesia, with or without IVT, does not adequately control disease. Furthermore, both TURBT and general anesthesia can be associated with complications in the elderly NMIBC population (Section 2.1.2.3). Alternative therapies for LG-IR-NMIBC ablation are needed that are safe, provide a durable complete response and durability of response, and reduce the need for repetitive TURBTs and general anesthesia.

#### *2.1.2.2 Post-TURBT Recurrence and Progression of LG-IR-NMIBC*

More than half of patients with IR-NMIBC will have disease recurrence after SoC TURBT ± IVT, suggesting that current SoC does not adequately control the disease.[20] A recent study of

patients with newly diagnosed IR-NMIBC found that 53% had at least 1 recurrence after 5 years of follow-up.[20] Recurrence-free intervals consistently decreased with each recurrence, with a median time to first, second, and third recurrence of 49, 19, and 12 months, respectively.[20] Patients with a European Organisation for Research and Treatment of Cancer (EORTC) recurrence risk score of 5 to 9 had a 1-year recurrence-free survival rate of ~60% following TURBT ± IVT, which dropped to ~33% at 2 years.[20] This means that two thirds of these patients required another surgery within 2 years. A meta-analysis of 7 NMIBC studies found that the 5-year probability of tumor recurrence following TURBT ± IVT ranges from 46% to 78% depending on a variety of risk factors.[21] The wide range of reported recurrence rates is likely due to substantial differences in patient characteristics (e.g., whether disease was recurrent and whether multiple tumors were present), variable use of IVT, and how the data were analyzed.

The reasons for the unacceptably high rate of recurrence following TURBT are multifactorial.[15,22-27] Incomplete tumor resection from primary TURBT is common because surgeons can only remove visible tumors. Consequently, residual tumor is found in 30% to 44% of cases up to 8 weeks after surgery.[28,29] Part of the reason for the failure of TURBT is that bladder cancer tends to present as a multifocal field defect. Removal of what is visible may not remove all tumor present because normal-appearing urothelium may have evidence of malignant transformation. Therefore, the current surgical management of NMIBC cannot effectively address the source of disease in many patients because it only removes the macroscopic manifestation and thus indirectly contributes to disease recurrence. Tumor-cell seeding during TURBT, low adoption of IVT, and poor compliance with surveillance protocols have also been proposed to contribute to high recurrence rates.[15,26,27,30]

Although disease recurrence following TURBT ± IVT is common in LG-IR-NMIBC, disease progression rates for LG disease are generally low.[4] Across studies, the progression rate by stage was approximately 1.1% at 1 year and 2.4% to 4.5% at 3 years, and the progression rate by grade (or unspecified) ranged from 5.1% to 6.9% at 1 year and from 4.5% to 8.6% at 3 years.[31-34] In a US prospective study where 145 patients had LG-IR-NMIBC, patients had a 2.8% rate of tumor stage progression and a 2.1% rate of tumor grade progression at a mean follow-up of 38 months.[25] The study also showed that the risk of progression increased with the greater number of recurrences during the follow-up period.[25]

#### *2.1.2.3 Procedural Risks, Morbidity, and Impact on Quality of Life*

TURBT can be associated with serious complications, including bleeding, bladder perforation, infection, and mortality.[35-39] Concerningly, repetitive TURBTs performed under general anesthesia are associated with an increased risk of death in patients with LG-NMIBC.[40] A longitudinal study of patients with LG-NMIBC found that, compared with those who only had a single TURBT, risk of death was increased by 14.3% in patients who had 2 to 4 TURBTs and by 27.5% in those who had ≥8.[40] Also, the risks of general anesthesia and TURBT are greater in the general NMIBC population because of age and the higher rate of comorbidities, including the need to stop anticoagulant medication.[41-43] TURBT is associated with anesthesia-related

adverse events (AEs) such as cognitive defects (transient delirium) and cardiopulmonary events.[41]

Patients with LG-IR-NMIBC experience a high burden of ongoing surveillance and repeated TURBT under general anesthesia, which can adversely affect their health-related quality of life (QoL) and carry a high psychosocial burden.[4,12,44-46] Across studies conducted globally, detrimental effects on QoL, including increased anxiety and impaired physical functioning and mental health, are reported by patients undergoing repeated TURBT or other surveillance procedures.[44-46] New therapeutic options for tumor ablation that reduce the need for repetitive surgeries and general anesthesia are crucially needed.[3,47]

The FDA's Position: The FDA agrees with the Applicant's position with respect to the diagnosis, management, and surveillance of NMIBC. Regarding the risk of post-TURBT recurrence and progression of LG-IR-NMIBC, the FDA notes that the cited literature reports on heterogenous patient populations with varied treatment practices and definitions of intermediate risk. In the recurrent LG-IR-NMIBC population that the Applicant enrolled in ENVISION, it is unclear which patients may subsequently have multiple recurrences vs. those who may have few recurrences or may never recur altogether after treatment with UGN-102. The Applicant also acknowledges this challenge in assessing recurrence risk with the following statement above: "*The wide range of reported recurrence rates is likely due to substantial differences in patient characteristics (e.g., whether disease was recurrent and whether multiple tumors were present), variable use of IVT, and how the data were analyzed."*

The Applicant's reference #20 (Sankin et al.) is used to support the statement that "more than half of patients with IR-NMIBC will have disease recurrence" after standard of care treatment. The FDA review team notes that this manuscript[1] states that this study was funded by UroGen Pharma, the Applicant. Additionally, it appears to be a retrospective review and recurrence-free survival, a time-to-event endpoint reported in this manuscript, is uninterpretable unless assessed in a randomized clinical trial. Thus, the FDA cannot agree to the Applicant's claims regarding recurrence risk derived from this report.

FDA agrees that repeated TURBT procedures may predispose patients to increased cumulative risk of certain adverse events. However, these risks must be considered in the context of an individual patient's performance status, co-morbidities, the number of TURBT procedures a patient may require, and their overall risk tolerance.

### 2.1.3 Product Description and Scientific Rationale for Development

The Applicant's Position:

UGN-102 (mitomycin) for intravesical solution is a reverse thermal gel formulation of mitomycin being developed as a nonsurgical treatment for recurrent LG-IR-NMIBC. The active drug component of UGN-102 is mitomycin, an entity approved in the United States since 1974.[48] Mitomycin is an alkylating drug that inhibits the synthesis of DNA. The guanine and

cytosine content correlates with the degree of mitomycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.[49]

UGN-102 is administered via urethral catheter in an office-based setting as a liquid under chilled conditions and transforms into a semisolid gel at body temperature to create a drug depot in the urinary bladder. General anesthesia is not needed, and the procedure allows patients to resume their daily routine immediately following the procedure. The gel slowly disintegrates over a period of up to 6 hours, with normal urine flow, enabling prolonged exposure of tumor sites and adjacent areas to high concentrations of mitomycin. The reverse thermal properties of the hydrogel and the method of administration optimize drug delivery while minimizing systemic drug exposure and systemic effects. In contrast to TURBT, UGN-102 has the potential to treat tumors too small to visualize via its field effect. UGN-102 is alternative pharmacotherapy for the treatment of LG-IR-NMIBC that can be used in selected patients to delay disease recurrence and reduce the burden of repeated TURBTs under general anesthesia.

UGN-102 is similar to JELMYTO® (mitomycin) for pyelocalyceal solution, which was also developed by UroGen. JELMYTO is FDA approved for treatment of adult patients with low-grade upper tract urothelial carcinoma (LG-UTUC), a malignancy that is histologically and clinically similar to urothelial bladder cancer but is localized to the renal pelvis and/or the ureters. JELMYTO was approved in 2020 as a breakthrough therapy and provides proof of concept (POC) for the mitomycin reverse thermal gel technology used in UGN-102. The approval of JELMYTO was based on the single-arm Phase 3 trial, OLYMPUS (NCT02793128), with a primary endpoint of complete response rate (CRR) at 3 months and secondary endpoint of duration of response (DOR) at 12 months.

The FDA's Position: The FDA agrees with the Applicant's position regarding characterization of the drug, the administration of the drug, and the cited regulatory history.

### 2.1.4 Product Development Program and Regulatory History

The Applicant's Position:

As a 505(b)(2) application, the Sponsor is relying on the Agency's findings of efficacy and safety for the reference listed drug Mutamycin® (mitomycin) for injection (NDA 050450) and on new information generated by the Sponsor during clinical trials to establish the efficacy and safety of a new formulation and use for mitomycin, UGN-102. Mutamycin was approved in the United States in 1974 for the treatment of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed.[49]

Data from 4 late-stage clinical trials support the approval of UGN-102 at the target dose (established in 4 early-stage studies) for the treatment of recurrent LG-IR-NMIBC. The UGN-102 late-stage clinical development program consists of the pivotal Phase 3 single-arm trial, ENVISION (BL011), and 3 supportive studies: a Phase 2b POC study for the use of mitomycin gel

technology in the bladder, OPTIMA II (BL005); a Phase 3 randomized controlled study of UGN-102 versus TURBT, ATLAS (BL006); and a small Phase 3b study that demonstrated the feasibility of home instillation of UGN-102 (BL010). For the complete summary of the UGN-102 clinical development program, see Appendix 1.

A summary of key regulatory interactions with the US FDA is provided in Appendix 2. The Sponsor and FDA never fully agreed on several aspects of the design of ATLAS, including the FDA requirement to demonstrate superiority of UGN-102 to a surgical procedure, the hybrid nature of the experimental arm (UGN-102 ± TURBT), and the definition of the primary disease-free survival (DFS) endpoint. At a Type C meeting held in August 2021, alternative development pathways were discussed, and the Agency stated that a single-arm study could serve as a major trial to support approval of UGN-102 if it enrolled a large number of patients, included sufficient duration of follow-up, and demonstrated sufficient efficacy and safety that encompassed outcomes with later TURBTs. It was agreed that the study population would consist of patients with recurrent LG-IR-NMIBC, that the primary and major secondary endpoints would be CRR and DOR, respectively, and that all efficacy analyses should be based on central pathology review. ENVISION satisfies all of the criteria specified for a single-arm trial to support the approval of UGN-102. Further justification for the pivotal study design is presented in Appendix 3.

The FDA's Position: The FDA recommended a randomized trial design to the Applicant several times during their product's development due to concerns with interpreting efficacy results and distinguishing whether any observed efficacy would be due to the investigational therapy or the natural history of the disease, as well as concerns with lack of comparative safety data against a concurrent control. The Applicant initiated a randomized clinical trial, ATLAS, in January of 2021. The Applicant and FDA did not find consensus on the design of ATLAS prior to its initiation due to disagreements regarding different definitions of DFS to be used in each arm and other design features proposed by the Applicant (see Section 2.2.3).

The FDA did eventually communicate to the Applicant that a single-arm design could potentially serve as a major trial to support approval of UGN-102 if it enrolled a large number of patients, had sufficient duration of follow-up, and demonstrated sufficient efficacy and safety that encompassed outcomes with later TURBTs. The FDA further stated that demonstrating treatment effect that is distinct from the natural history of disease would be critical, safety results would be considered, and the proposed follow up of 18 months after response may not capture durability adequately. Lastly, the FDA noted to the Applicant that an NDA supported by data generated in a single arm trial would likely require discussion at ODAC. After further discussion with FDA, the Applicant chose to terminate the ATLAS trial early and pursue a single-arm trial design instead.

The FDA considers the single arm study BL011 (ENVISION) to be the primary source of data to support a claim of effectiveness and considers the randomized study BL006 (ATLAS) supportive. The FDA review team has considered safety data from Study BL010, but not efficacy data, due

to the limited sample size in this study and other potential differences related to a population treated with at-home instillations. The FDA does not consider the data from the OPTIMA II trial to be supportive evidence. OPTIMA II was a small, single-arm, proof-of-concept trial which differed from the pivotal ENVISION trial in several key aspects. The patient population enrolled in OPTIMA II included both newly diagnosed and recurrent LG-NMIBC patients, differing from the recurrent-only population enrolled in ENVISION (See Section 2.2.2.1 below). The primary and secondary endpoint of CRR at 3 months and DOR were based on disease assessment (biopsy and cytology) per local review.

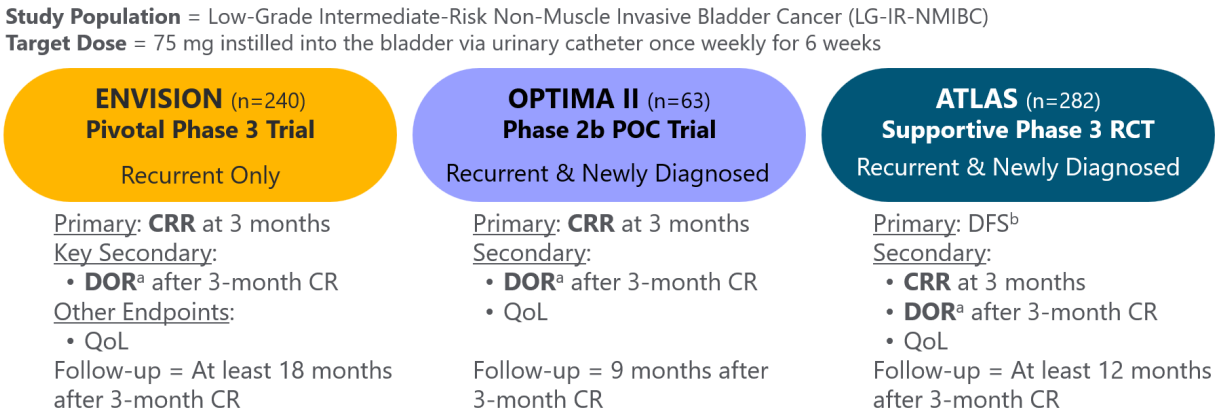
The FDA notes that although central pathology review was protocol-defined as the method for disease assessment, disease for several patients in the trials proposed to support the intended use (i.e., ENVISION and ATLAS) were instead evaluated only by local pathology (See Section 2.2.1.1 for further details).

## 2.2 Summary of Clinical Trials Supporting Efficacy

The Applicant's Position:

The efficacy of UGN-102 for the treatment of patients with recurrent LG-IR-NMIBC was established in ENVISION, and supportive data are provided by OPTIMA II and ATLAS (Figure 1). The age, sex, and race/ethnicity of the study populations are reflective of the general NMIBC population in the United States (Section 2.1.1). The patient population was defined the same across all late-phase studies except that ENVISION enrolled patients only with recurrent LG-IR-NMIBC, whereas OPTIMA II and ATLAS enrolled patients with either newly diagnosed or recurrent disease. For key inclusion and exclusion criteria, please see Appendix 4. All studies evaluated the target dose regimen of 75 mg delivered via urinary catheter once weekly for 6 weeks. Evaluation of response was based on standard urological practice (white light cystoscopy, histopathology, urine cytology) and the definition of complete response (CR) and DOR was the same in all studies. CR was defined as a negative cystoscopy and urine cytology, and, when indicated, a negative for-cause biopsy. DOR was determined by Kaplan-Meier (KM) estimate and defined as the time from the first documented CR to the earliest date of recurrence or progression as determined using the date of cystoscopy, for-cause biopsy, cytology, or death due to any cause, whichever occurred first.

**Figure 1 Overview of the UGN-102 Late-Phase Studies**




[a]Estimated by KM method. Defined as time from 3-month CR to first recurrence of LG disease, progression, or death due to any cause.
[b]Time from randomization to residual LG disease at 3 months in the TURBT arm, recurrence of LG disease after 3 months, progression at any time, or death due to any cause.
CR=complete response; CRR=complete response rate; DFS=disease-free survival; DOR=duration of response; IR=intermediate risk; KM=Kaplan-Meier; LG=low grade; NMIBC=non-muscle invasive bladder cancer; POC=proof of concept; QoL=quality of life; RCT=randomized clinical trial; TURBT=transurethral resection of bladder tumor.

The FDA's Position: The FDA considers ENVISION to be the primary source of data to support an efficacy claim. Since this trial enrolled patients with recurrent disease only, the FDA's review focuses on this population for any purported efficacy claim. The FDA notes that the ATLAS trial was terminated early and had several design flaws that limit interpretability of results from this study. However, the FDA conducted exploratory efficacy and safety analyses from ATLAS, which enrolled a population partially overlapping with that of ENVISION and considered this study to be supportive. The FDA does not consider OPTIMA II to be supportive of an efficacy claim for the reasons discussed in Section 2.1.4 above.

### 2.2.1 Pivotal Phase 3 Study ENVISION

The Applicant's Position:

ENVISION is evaluating the efficacy and safety of UGN-102 as primary chemoablative therapy in adult patients with recurrent LG-IR-NMIBC. Enrollment is completed, and the study is ongoing. Final data are reported for the primary endpoint (CRR at 3 months). Secondary and exploratory efficacy endpoints are reported through a data cutoff (DCO) date of October 2, 2024, which includes a minimum of 18 months of follow-up after the 3-month Visit (through at least Study Month 21) for ongoing patients.

ENVISION was designed following discussions with the FDA to serve as the basis for approval of UGN-102. ENVISION enrolled patients with recurrent LG-IR-NMIBC, the subpopulation with the highest unmet need for a new treatment option, because TURBT ± IVT has already failed in these patients. In accordance with criteria outlined by the FDA for a single-arm study to support

approval of UGN-102, ENVISION enrolled a large number of recurrent patients, CRR and DOR were considered in the sample size calculation, patients have a sufficient duration of follow-up, and outcomes of subsequent TURBTs have been evaluated and found to have no increased rates of complications. Available results demonstrate clinically meaningful efficacy and safety and a positive benefit–risk profile for UGN-102 in the treatment of adults with recurrent LG-IR-NMIBC.

#### *2.2.1.1 Study Design and Methods*

ENVISION is an open-label, single-arm, multinational, Phase 3 study. Participants received UGN-102 (75 mg mitomycin) once weekly via intravesical instillation for 6 weeks (Figure 2). At the 3-month Visit, patients who had a CR entered the Follow-up Period of the study. Patients who had a non-complete response (NCR) due to residual LG disease underwent investigator-designated SoC treatment of remaining lesions and then entered the Follow-up Period.

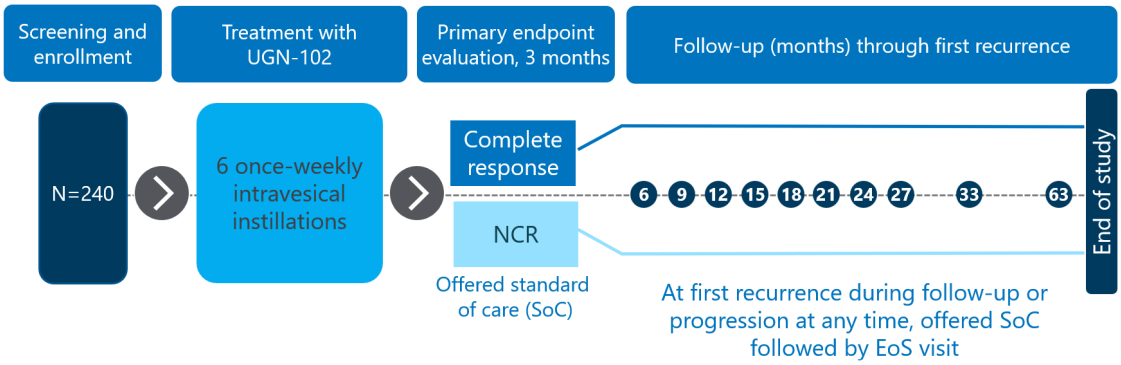
During the Follow-up Period, patients return to the clinic for evaluation of response every 3 months for up to 24 months (27 months after the first instillation). Patients who remain disease free at the 27-month Visit will continue to be followed every 6 months for up to 36 months (63 months after the first instillation) or until disease recurrence, disease progression, death, or the study is closed by the Sponsor, whichever occurs first.

Patients who have a disease recurrence during the Follow-up Period or disease progression at any time undergo investigator-designated SoC treatment and have a separate end-of-study Visit performed 3 months after SoC.

The primary objective of the study is to evaluate CRR at the 3-month Visit. The key secondary objective is to evaluate DOR by KM estimate. Other secondary objectives include evaluation of durable complete response (DCR) rates at scheduled disease assessments. DCR rate is defined as the proportion of patients who achieve a CR at the 3-month Visit and maintain a CR up to a particular follow-up disease assessment. Exploratory QoL endpoints include patient-reported outcomes (PROs) and qualitive patient preference interviews (Section 4.1).

The sample size was determined based on assumptions regarding CRR and 12-month DOR in this population. For detailed information on the statistical analysis methods, see Appendix 5.

**Figure 2 ENVISION Study Design**




Complete response defined as negative white-light cystoscopy, negative urine cytology, and, when indicated, a negative for-cause biopsy. Progression defined as an increase in grade or stage compared to baseline. SoC offered was investigator-designated.
EoS=end of study; NCR=non-complete response; SoC=standard of care.

ENIVISION is a rigorously conducted multiregional trial. Patients were enrolled at 56 sites in 10 countries (US and Europe), and 25% of study sites were in the United States. Among 14 enrolling study centers in the United States, all are in urban locations, defined as having a population of at least 5,000 per the US Census Bureau,[50] including 9 (64%) community cancer centers and 5 (36%) academic centers. All investigators at all study sites were urologists with appropriate qualifications and experience in conducting clinical trials. Investigators were instructed not to resect tumor during the diagnostic biopsy and were required to document the presence of residual tumor after biopsy and before UGN-102 treatment. The study procedures used to evaluate response to UGN-102 treatment, including cystoscopy and biopsy, are standard urological procedures across regions. Biopsies, urine cytology, and blood tests performed during the study were reviewed at a central laboratory except in a few cases where it was not feasible. In such situations, a local laboratory was used.

The FDA's Position: The FDA agrees with the Applicant's description of the ENVISION trial design.

While the Applicant notes that biopsies were reviewed at a central laboratory with few exceptions due to feasibility, this applied only to the disease assessments (3-month assessment and onwards), as the protocol allowed for enrollment eligibility based on either local pathology or central pathology review. One-hundred and forty-nine patients (67%) were initially enrolled based on local pathology review. The remainder, 74 (33%) patients, were initially enrolled based on central pathology review. All 37 biopsies performed at the 3-month assessment underwent central pathology review. In follow up beyond the 3-month assessment, 43 patients had at least one biopsy with a diagnostic assessment. Of those 43 patients, 40 patients (93%) underwent central review and 3 patients (7%) underwent only local pathology review.

The FDA reviewed outcomes in patients who received local or central pathology at screening

and/or at disease assessments and results for both CR and DOR appeared consistent regardless of whether central or local pathology was used at screening/follow-up.

For the secondary endpoint of DOR, the KM method is generally not used by FDA to estimate the durability of CR at a landmark time point, as the KM assumptions may overestimate the proportion of patients who remained in CR, particularly when follow-up is limited. Instead, the FDA evaluates the observed proportion of patients who remained in CR at the landmark time point, considering only those who were still being followed and confirmed to be in CR at that specific time.

For another secondary endpoint, DCR, the discrepancy between the FDA analysis and Applicant's reported DCR proportion is mainly due to how follow-up timing was handled. The FDA used the exact timing of events or censoring, while the Applicant grouped data by scheduled visit windows, each spanning a 90-day period. Additionally, the Applicant used imputed data for DCR analysis, though this only affected the results for a small number of patients. However, the imputation approach was generally optimistic.

Patient-reported outcomes (PROs) and qualitive patient preference interviews are challenging to interpret due to the single-arm study design. See Section 4 for discussion of PROs.

### 2.2.2 Supportive Phase 2b Study OPTIMA II

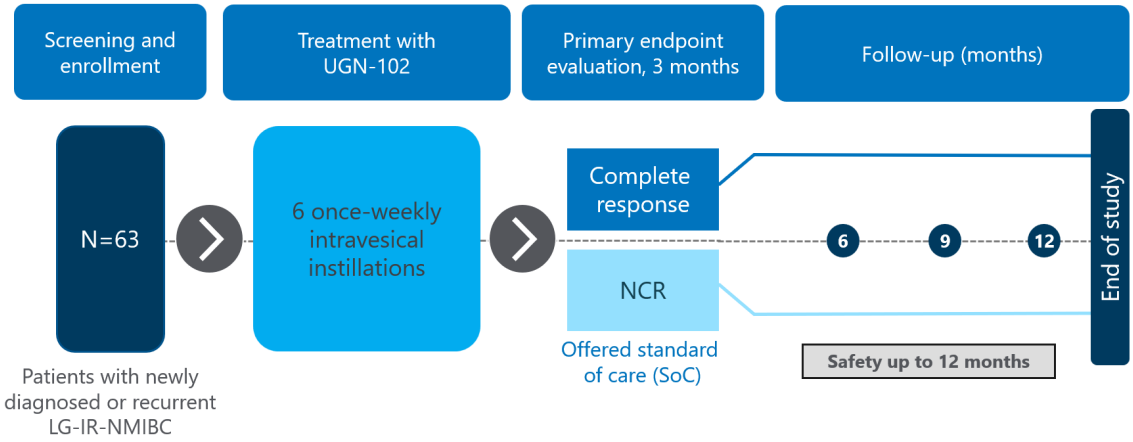
The Applicant's Position:

OPTIMA II evaluated the efficacy and safety of UGN-102 as a primary chemoablative treatment in adult patients with newly diagnosed or recurrent LG-IR-NMIBC.

#### *2.2.2.1 Study Design and Methods*

Patients received UGN-102 (75 mg mitomycin) once weekly via intravesical instillation for 6 weeks in an office setting (Figure 3). The chemoablative effect of UGN-102 was assessed 3 months after the start of treatment, with CR as the primary endpoint. Patients who achieved a CR at 3 months were followed every 3 months for up to 9 months post CR (12-months from initial treatment) to evaluate durability of response.

**Figure 3 OPTIMA II Study Design**




Complete response determined by cystoscopy, urine cytology, and for-cause biopsy.
IR=intermediate risk; LG=low grade; NCR=non-complete response; NMIBC=non-muscle invasive bladder cancer; SoC=standard of care.

The FDA's Position:
The FDA does not consider the data from the OPTIMA II trial to be supportive evidence. OPTIMA II was a small single-arm, proof-of-concept trial which differed from the pivotal ENVISION trial in several key aspects. The patient population enrolled in OPTIMA II included both newly diagnosed and recurrent LG-NMIBC patients, differing from the recurrent-only population enrolled in ENVISION.

Disease assessments (biopsies and urine cytology) to define the primary and key secondary endpoint of CR at 3 months and DOR were conducted by local review instead of central review. Follow-up in OPTIMA II was limited to only 9 months following determination of CR, which renders estimation of DOR challenging.

### 2.2.3 Supportive Phase 3 Study ATLAS

The Applicant's Position:

#### *2.2.3.1 Study Design and Methods*

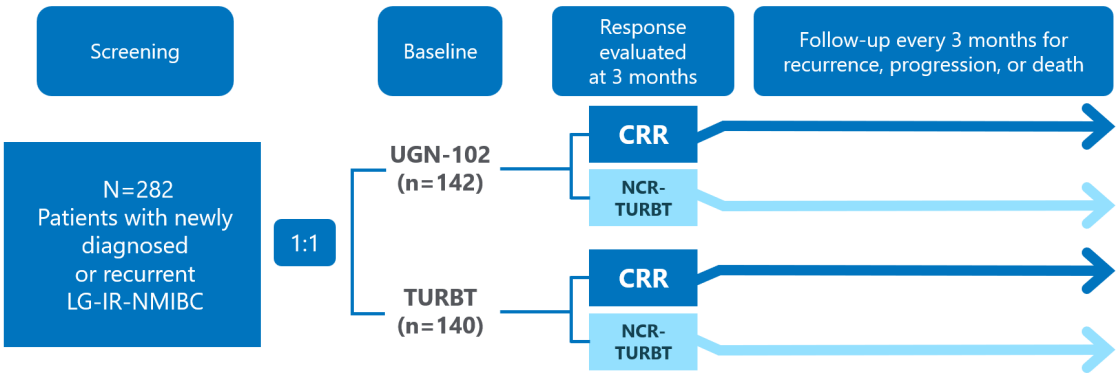
ATLAS was a multinational, randomized, controlled, open-label, Phase 3 trial that assessed the efficacy and safety of UGN-102 with or without TURBT for the presence of residual disease at 3 months (UGN-102 ± TURBT) versus TURBT at baseline with or without TURBT for the presence of residual disease at 3 months (TURBT alone) for the treatment of adult patients with newly diagnosed or recurrent LG-IR-NMIBC. TURBT was chosen as the comparator arm because it most closely reflects current US community-based management of LG-IR-NMIBC. Eligible patients were randomized in a 1:1 ratio to receive UGN-102 or TURBT at baseline (Figure 4). Randomization was stratified by the presence (yes or no) of a previous LG-NMIBC episode within 1 year of the current diagnosis. Starting on Day 1, patients randomized to the UGN-102

arm received UGN-102 (75 mg mitomycin) once weekly via intravesical instillation for 6 weeks in an office setting, and patients randomized to the TURBT-alone arm underwent TURBT.

All patients returned to the clinic approximately 3 months after the start of treatment for a disease assessment visit. Patients confirmed to have a CR received no further treatment and entered the Follow-up Period of the study. Patients confirmed to have an NCR due to residual LG disease in either arm underwent TURBT of any remaining lesions and then entered the Follow-up Period. Patients confirmed to have an NCR due to disease progression were considered to have completed the study and released to the care of their treating physician.

During the Follow-up Period, patients were assessed for response every 3 months through Month 15 or until disease recurrence, progression, or death was documented, whichever occurred first.

**Figure 4 ATLAS Study Design**




Complete response was defined as negative white-light cystoscopy, negative urine cytology, and, when indicated, a negative for-cause biopsy. Progression was defined as an increase in grade or stage compared to baseline.
Prasad SM, et al. *J Urol*. 2023;210(4):619-629.[51]
CRR=complete response rate; IR=intermediate risk; LG=low grade; NCR=non-complete response; NMIBC=non-muscle invasive bladder cancer; SoC=standard of care; TURBT=transurethral resection of bladder tumor.

The primary endpoint, DFS, examined the impact of a hybrid intervention: UGN-102 at baseline, plus TURBT at 3 months for the presence of residual disease, versus TURBT alone. DFS was defined as the time from randomization until the earliest date of any of the following events: failure to be rendered free of local disease at the 3-month Visit in the TURBT-alone arm, recurrence (or persistence) of LG disease after the 3-month Visit (i.e., during the Follow-up Period), progression to HG disease, or death due to any cause. Residual disease at the 3-month Visit in the UGN-102 ± TURBT arm was not considered a DFS event in the protocol-specified analysis because patients had not completed the prespecified hybrid intervention. Progression to HG disease at any time during the study (including at the 3-month Visit) was considered a DFS event in both arms. See Section 2.3.3.3 for further discussion of the DFS endpoint.

The secondary endpoints were CRR at the 3-month Visit, DOR, and DCR rates at follow-up disease assessments. Thus, 3-month CRR, DOR, and DCR from ATLAS serve as supportive data to the corresponding primary and secondary endpoints in the pivotal trial, ENVISION. In ATLAS, CRR, DOR, and DCR were measured in patients who received only the baseline intervention and therefore provide direct comparisons of treatment with UGN-102 alone versus TURBT. TURBTs done at 3 months for residual LG disease did not impact measurement of CRR, DOR, or DCR.

Avoidance of TURBT was also a secondary endpoint in ATLAS. Specifically, the proportion of patients requiring TURBT in each arm and the average number of TURBT interventions per patient in each arm were prespecified endpoints. These measurements provide an assessment of the reduction in overall burden of TURBT associated with UGN-102 treatment.

The Sponsor and the FDA never fully agreed on several aspects of the design of ATLAS, including the FDA requirement to demonstrate superiority of UGN-102 to a surgical procedure, the hybrid nature of the experimental arm, and the definition of the primary DFS endpoint. Following agreement with the FDA in 2021 that a single-arm trial (ENVISION) could be the basis for approval of UGN-102, patient accrual in ATLAS was suspended at 282 participants (45% of planned) without knowledge of the data. The trial was continued until all ongoing patients had completed at least 12 months of follow-up after the 3-month Visit. A total of 19% of planned events were observed for the primary DFS endpoint, with a median follow-up of 15 months in both arms. ATLAS is a supportive study with secondary endpoints that provide a randomized comparison of UGN-102 to community-based care for LG-IR-NMIBC (TURBT) and facilitate the assessment of consistency of UGN-102 efficacy results (CRR, DOR, and DCR) across the development program.

The FDA's Position: The FDA agrees with the Applicant's description of the ATLAS trial design. However, the review team notes the following:

- ATLAS did not allow for receipt of a single post-operative instillation of intravesical chemotherapy for patients in the control arm (TURBT alone). This adjunct has demonstrated a reduced risk of recurrence of ~35% in subpopulations of patients with intermediate-risk NMIBC, particularly those with small (<3 cm) and solitary tumors.[2-4] Therefore, the FDA considers that the control arm therapy received would not be consistent with expert consensus guideline-recommended care in the U.S for some patients enrolled on ATLAS.
- The FDA did not agree with the differential definition of DFS between arms, where residual disease at the 3-month assessment in the UGN-102 ± TURBT arm was not considered a DFS event but was considered a DFS event in TURBT arm. The definition of DFS events should be applied consistently across both arms to ensure that the observed treatment effect is attributed to the true differences in the treatment rather than discrepancies in the event definition.
- Prior to terminating the trial, ATLAS was designed as a non-inferiority study with the primary endpoint of DFS to be tested hierarchically for non-inferiority followed by

superiority. The FDA did not agree with the non-inferiority design with DFS as the primary endpoint. In general, non-inferiority trials with time-to-event endpoints other than overall survival are not appropriate. It is challenging to establish an appropriate non-inferiority margin in this setting. In addition, the handling of NCR patients in the UGN-102 arm may show that two inherently different treatments are similar using DFS.

- When ATLAS was terminated early by the Applicant, the statistical analysis plan was modified such that the study was no longer powered to perform hypothesis testing, and all analyses would be descriptive in nature. The FDA was not consulted by the Applicant for the decision making of early termination of ATLAS. The Applicant has stated that they terminated ATLAS due to a "financial decision" and to pursue a single arm trial design instead.
- The FDA does not find the reported results based on the pre-specified primary analysis from ATLAS to be interpretable, however the review team did conduct exploratory analyses of CRR as discussed further below. The early termination of the trial complicates the interpretation of DOR due to limited follow up.
- The issues related to DOR KM estimates at landmark time points and DCR at specific disease follow-up assessments described in ENVISION also apply to ATLAS.

## 2.3 Efficacy Summary

The efficacy of UGN-102 in both newly diagnosed and recurrent LG-IR-NMIBC was evaluated in the intent-to-treat (ITT) Analysis Population. In alignment with FDA, all efficacy analyses are presented for the FDA Analysis Population (Table 1). Across studies, that population includes all treated patients who met the per-protocol definition of LG-IR-NMIBC, had recurrent disease (defined as a history of LG-NMIBC treated with TURBT), and had no major protocol deviation that would confound the efficacy evaluation. Data from the ITT Analysis Population, which, per study protocol, included all treated patients in ENVISION and OPTIMA II and all randomized patients in ATLAS, are provided in Appendix 6.

**Table 1 Summary of Analysis Populations**

| | UGN-102 | | | TURBT |
|---|---|---|---|---|
| Population | ENVISION (N=240) n (%) | OPTIMA II (N=63) n (%) | ATLAS (N=142) n (%) | ATLAS (N=140) n (%) |
| ITT Analysis Population | 240 (100) | 63 (100) | 142 (100) | 140 (100) |
| FDA Analysis Population | 223 (92.9) | 47 (74.6) | 51 (35.9) | 57 (40.7) |

ITT=Intent-to-treat; TURBT=transurethral resection of bladder tumor.
Source: ISE-FDA Analysis Set-Table 14.1.1a

### 2.3.1 Pivotal Phase 3 Study ENVISION Results

The Applicant's Position:

#### 2.3.1.1 *Demographics and Baseline Disease Characteristics*

A total of 240 patients were enrolled and treated with UGN-102 in ENVISION, of whom 223 were included in the FDA Analysis Population. The median age of patients was 70.0 (range, 30-92) years. Most patients were male (62.3%), White (97.8%), and not Hispanic or Latino (98.7%).

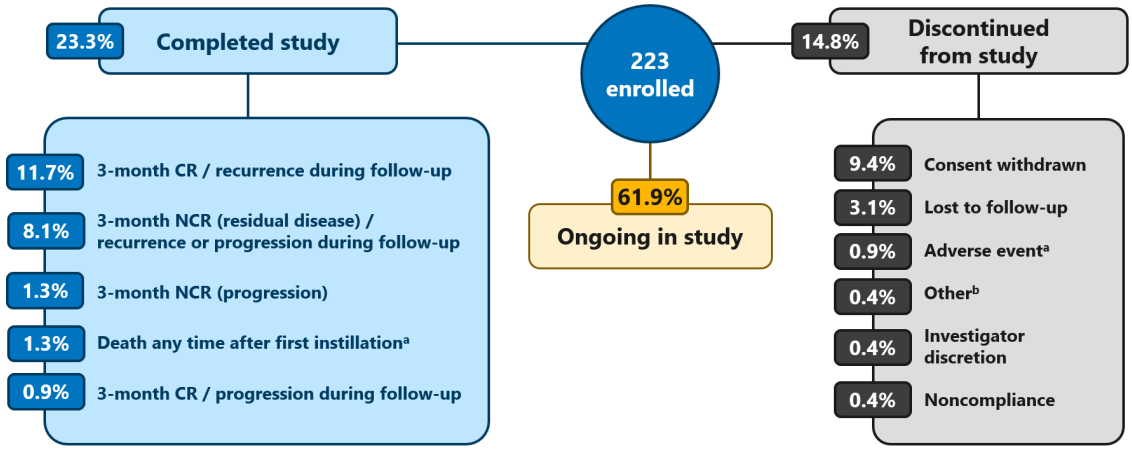
Overall, 212 of 223 patients (95.1%) completed all 6 planned instillations of UGN-102. All patients had a previous LG-NMIBC episode and a prior TURBT for LG-NMIBC, and 36.3% of patients had ≥2 previous LG-NMIBC episodes. More than half of patients had a previous LG-NMIBC episode within 1 year of the current diagnosis (54.7%). At baseline, most patients had multiple tumors (84.7%), with a longest tumor diameter ≤3 cm (93.6%) and total tumor burden ≤3 cm (82.4%), which is consistent with recurrent IR disease. More than half of patients (54.7%) were current or former smokers.

See Appendix 7 for a complete summary of demographics and baseline disease characteristics in the ENVISION FDA Analysis Population.

#### 2.3.1.2 *Patient Disposition*

As of the October 2, 2024, DCO date, 138 of 223 patients (61.9%) were ongoing in the study, 52 patients (23.3%) had completed the study, and 33 patients (14.8%) had discontinued the study (Figure 5). Among patients who completed the study, the main reasons were recurrence during follow-up in patients who had a CR (11.7%) or recurrence or progression due to residual disease in patients with an NCR (8.1%) at the 3-month Visit (Figure 5). Among patients who discontinued early from the study, the main reasons were withdrawal of consent (9.4%) and lost to follow-up (3.1%) (Figure 5). AEs leading to treatment or study discontinuation were low and are detailed in Section 3.3.

**Figure 5 Patient Disposition – FDA Analysis Population (ENVISION)**

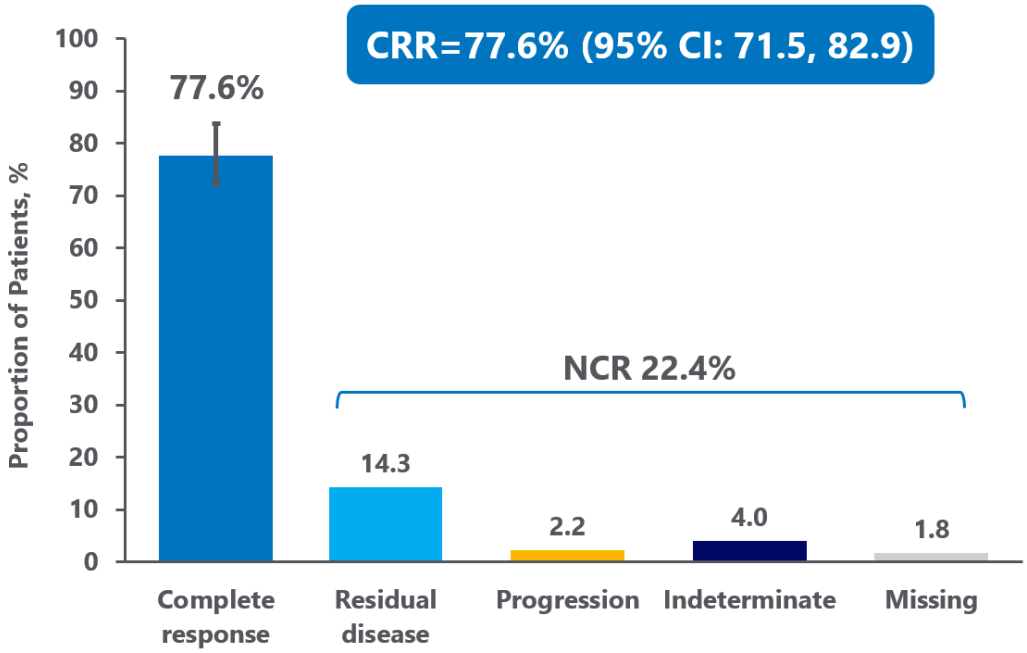



[a]Number of patients who discontinued from study due to adverse event does not include 3 patients with fatal TEAEs who are categorized as completed study due to death any time after first instillation.
[b]One patient with recurrence at Month 6 did not want to receive any of the offered standard treatment modalities.
CR=complete response; NCR=non-complete response; TEAE=treatment-emergent adverse event.
Source: BL011-M21-FDA Analysis Set-Table 14.1.4.2a

### *2.3.1.3 Primary Endpoint: CRR at 3 Months*

Of the 223 patients in the FDA Analysis Population, 173 (77.6%) achieved a CR at the 3-month Visit (95% confidence interval [CI]: 71.5, 82.9). The remaining 22.4% did not achieve a CR (NCR), mainly because of residual LG disease (Figure 6).

**Figure 6 Clinically Meaningful Complete Response Rate – FDA Analysis Population (ENVISION)**

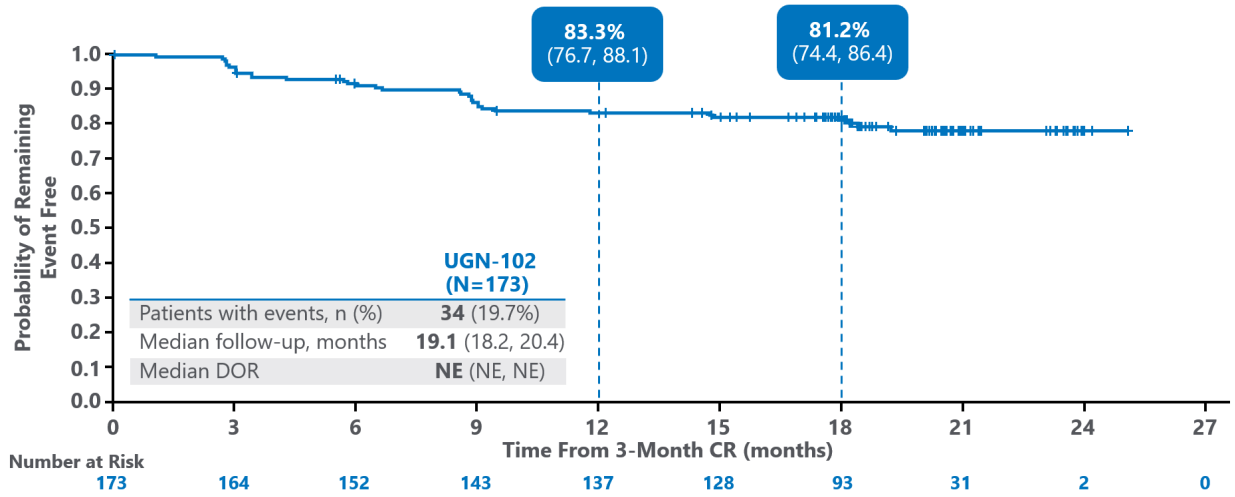



3-month CRR defined as the proportion of patients who achieved a CR at the 3-month Visit (3 months after the first instillation of UGN-102) as determined by cystoscopy, for-cause biopsy, and urine cytology.
CI=confidence interval; CR=complete response; CRR=complete response rate; NCR=non-complete response.
Source: BL011-M21-FDA Analysis Set-Table 14.2.1.1a

### *2.3.1.4 Secondary Endpoints: DOR and DCR Rate at 12 and 18 Months After 3-Month CR*

Among patients who achieved a CR at 3 months, UGN-102 was associated with a clinically meaningful DOR. The median follow-up was 19.1 months, and the median DOR was not estimable (Figure 7). At 12 months after 3-month CR, the probability of remaining event free by KM estimate was 83.3% (95% CI: 76.7, 88.1) (Figure 7). Durability of response was maintained at later time points, with a KM estimate of 81.2% (95% CI: 74.4, 86.4) at 18 months after 3-month CR (Figure 7).

**Figure 7** **Clinically Meaningful Duration of Response – FDA Analysis Population (ENVISION)**




DOR defined as the time from the first documented CR to the earliest date of recurrence or progression as determined using the date of cystoscopy, for-cause biopsy, cytology, or death due to any cause, whichever occurred first.
CR=complete response; DOR=duration of response; NE=not estimable.
Source: BL011-M21-FDA Analysis Set-Table 14.2.2.1d; Table 14.2.2.2d; Figure 14.2.2g

ENVISION demonstrated clinically meaningful DCR rates. DCR is an additional measure of durability that does not take into account censoring and is a more conservative estimate than DOR. Among 173 patients who had a CR at the 3-month Visit, 137 (79.2%) were directly observed to remain in CR 12 months after 3-month CR, and 123 (71.1%) were directly observed to remain in CR 18 months after 3-month CR (Table 2).

**Table 2** **Robust DCR Rates – FDA Analysis Population (ENVISION)**

| | UGN-102 (N=173) | |
|---|---|---|
| **Months After 3-Month CR** | **n** | **DCR Rate[a] (95% CI)** |
| 3 | 157 | 90.8 (85.4, 94.6) |
| 6 | 152 | 87.9 (82.0, 92.3) |
| 9 | 139 | 80.3 (73.6, 86.0) |
| **12** | **137** | **79.2** (72.4, 85.0) |
| 15 | 133 | 76.9 (69.9, 82.9) |
| **18** | **123** | **71.1** (63.7, 77.7) |

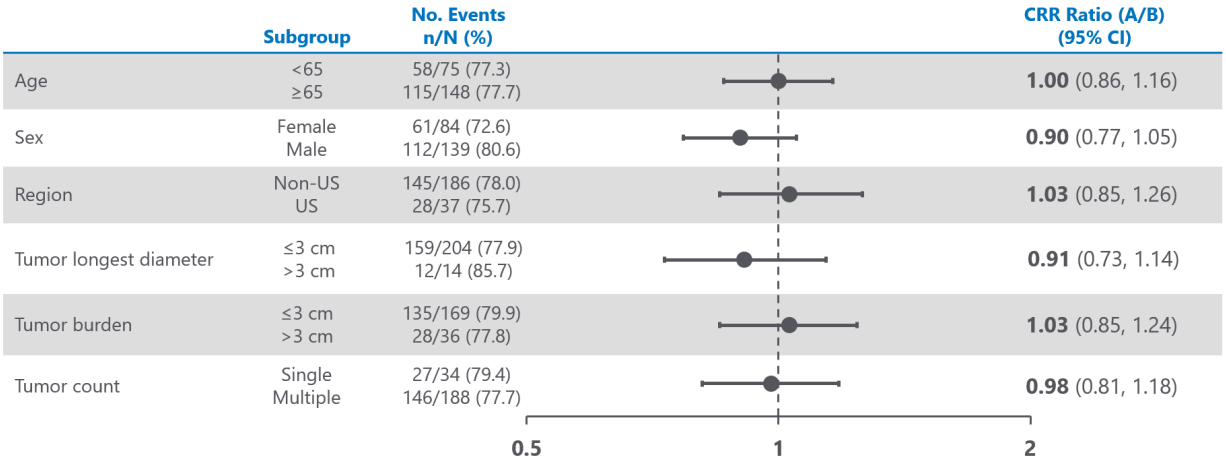
[a]DCR rate is the proportion of patients who achieved a CR at the 3-month Visit and maintained a CR up to a particular follow-up disease assessment.
CI=confidence interval; CR=complete response; DCR=durable complete response.
Source: BL011-M21-FDA Analysis Set-Table 14.2.3.1.1.3

### *2.3.1.5 Prespecified Subgroup Analyses*

Subgroup analyses for the primary endpoint, CRR, demonstrated consistent efficacy across baseline demographics and tumor prognostic factors, including age, sex, region, longest tumor diameter, total tumor burden, and tumor count (Figure 8).

A similar trend was observed in subgroup analyses of DOR across baseline demographics, except for region. DOR was lower in US patients than in non-US patients. A potential driver for this difference in ENVISION is previous NMIBC episodes. Most US patients in the DOR analysis had multiple prior recurrences and tended to have shorter DOR compared with those who had only 1 prior recurrence. Results of this subgroup analysis should be interpreted with caution, however, because Region was not a prespecified subgroup analysis in ENVISION, the sample size is small, and the subgroup analyses are not protected by randomization.

**Figure 8 Consistent Complete Response Rate Across Subgroups – FDA Analysis Population (ENVISION)**




CI=confidence interval; CRR=complete response rate; US=United States.
Source: BL011-M21-FDA Analysis Set-Table 14.2.1.3.1a; Dataset: BL011-M21-FDA Analysis Set-ADSL

The FDA's Position: The FDA agrees with the Applicant's description of the demographics, baseline disease characteristics, patient disposition, and the reported CR rate of 77.6% (95% CI: 71.5, 82.9). The FDA notes that our review identified 17 patients in the ENVISION trial that did not meet the protocol-defined eligibility criteria. The Applicant confirmed that these patients did not meet eligibility criteria in correspondence with the FDA during review. Thus, the FDA considers the efficacy evaluable population in ENVISION to be n=223.

As stated previously, the Applicant's estimations of durability in maintaining CR at landmark time points may be over-estimated. Based on FDA's analysis, the observed percentage of patients who were followed up and maintained CR was 79.2% (95% CI: 72.3, 85.0) at 12 months and was 53.8% (95% CI: 46.0, 61.4) at 18 months. Note that 28 patients were censored between 17 and 18 months of follow-up and, therefore, were not counted as maintaining CR at the 18-month time point, which likely contributed to the lower 18-month percentage compared to the Applicant's KM estimate and DCR at the 18-Month Visit.

In general, the FDA does not directly compare subgroups (e.g., CRR ratio) to assess for consistency in CRR across subgroups as shown by the Applicant in Figure 8. The FDA agrees that CRR is consistent across subgroups of relevant baseline demographics and disease

characteristics. The table below shows CRR subgroup analyses:

**FDA's Table 1. Subgroup Analyses of CRR in FDA Analysis Population (ENVISION)**

| Characteristics | Subgroup | No. CR/No. Patients | CRR (95% CI) |
|---|---|---|---|
| **Age** | < 65 | 58/75 | 77.3% (66.2, 86.2) |
| | ≥ 65 | 115/148 | 77.7% (70.1, 84.1) |
| **Gender** | Female | 61/84 | 72.6% (61.8, 81.8) |
| | Male | 112/139 | 80.6% (73.0, 86.8) |
| **Region** | US | 28/37 | 75.7% (58.8, 88.2) |
| | Non-US | 145/186 | 78.0% (71.3, 83.7) |
| **Tumor Count[a]** | Single | 27/34 | 79.4% (62.1, 91.3) |
| | Multiple | 146/188 | 77.7% (71.0, 83.4) |
| **Longest Tumor Diameter[b]** | ≤ 3 cm | 159/204 | 77.9% (71.6, 83.4) |
| | > 3 cm | 12/14 | 85.7% (57.2, 98.2) |
| **Previous LG-NMIBC within 1 Year** | Yes | 93/122 | 76.2% (67.7, 83.5) |
| | No | 80/101 | 79.2% (70.0, 86.6) |
| **Previous LG-NMIBC Episodes** | 1 | 112/142 | 78.9% (71.2, 85.3) |
| | 2 | 30/38 | 78.9% (62.7, 90.4) |
| | > 2 | 31/43 | 72.1% (56.3, 84.7) |

[a] One patient with missing tumor count at baseline had an NCR at the 3-month visit.
[b] Two out of five patients with missing longest tumor diameter at baseline had a CR at the 3-month visit.

FDA acknowledges the Applicant's position regarding DOR subgroup analyses and agrees that these should be interpreted with caution due to small sample sizes and lack of randomization.

The ability to undergo a subsequent TURBT did not appear to be substantially affected after treatment with UGN-102. TURBT was the most common subsequent procedure for those patients treated with UGN-102 who did not achieve a CR at the 3-month time point and had a standard of care procedure.

### 2.3.2 Supportive Phase 2b Study OPTIMA II Results

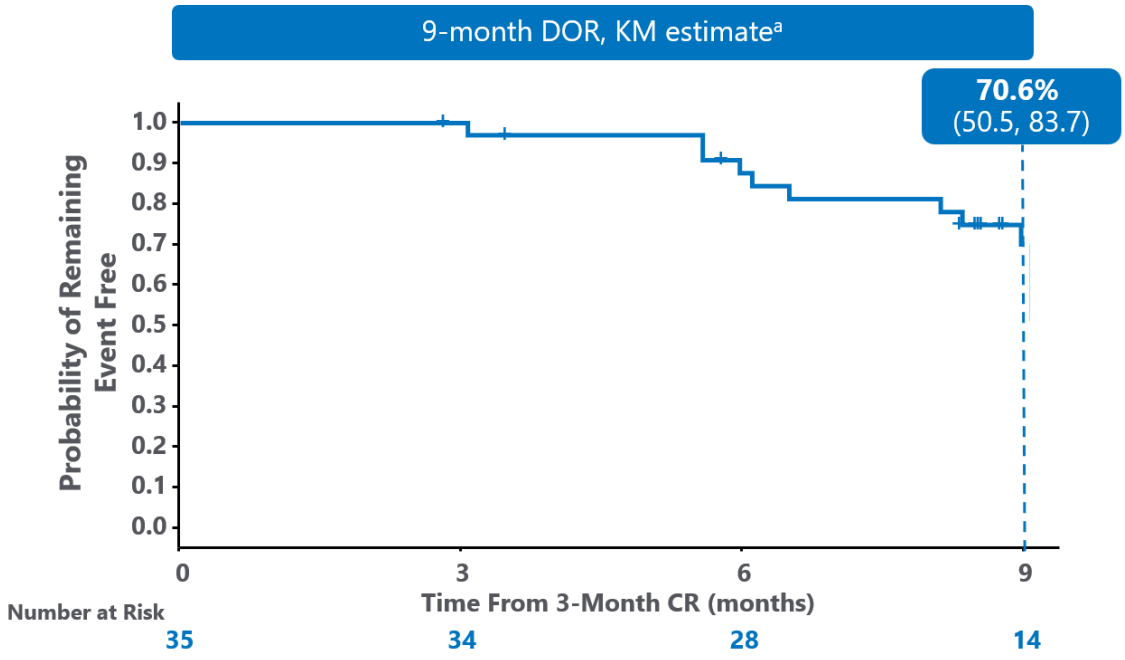
The Applicant's Position:

A total of 63 patients were enrolled and treated with UGN-102 in OPTIMA II, of whom 47 met the criteria for LG-IR-NMIBC and were included in the FDA Analysis Population. The median age of patients was 68.0 (range, 33-96) years. Most patients were male (55.3%), White (85.1%), and not Hispanic or Latino (95.7%).

Overall, 43 of 47 patients (91.5%) completed all 6 planned instillations of UGN-102. All patients had a previous LG-NMIBC episode and 78.7% had ≥2 episodes. All patients had a prior TURBT for LG-NMIBC. More than half of patients had a previous LG-NMIBC episode within 1 year of the current diagnosis (57.4%). At baseline, most patients had multiple tumors (84.8%), with a longest tumor diameter ≤3 cm (89.1%) and total tumor burden ≤3 cm (80.4%).

OPTIMA II established POC for UGN-102. Of the 47 patients in the FDA Analysis Population, 35 patients (74.5%) achieved a CR at the 3-month Visit (95% CI: 59.7, 86.1). The KM-estimated probability of remaining in response 9 months after 3-month CR (DOR) was 70.6% (95% CI: 50.5, 83.7) (Figure 9). Among the 35 patients with a CR at the 3-month Visit, 20 (57.1%) had a DCR at 9 months after the 3-month CR (95% CI: 39.4, 73.7).

**Figure 9 9-Month Duration of Response – FDA Analysis Population (OPTIMA II)**




[a]KM estimate of the probability that a patient will remain in CR 9 months after 3-month CR (12 months after treatment initiation).
CR=complete response; DOR=duration of response; KM=Kaplan-Meier.
Source: ISE-FDA Analysis Set-Table 14.2.2.1.2.1d; Dataset: ISE-FDA Analysis Set-ADTTE

The FDA's Position: As noted above, the FDA does not consider the data from the OPTIMA II trial to be supportive evidence.

The Applicant's estimations of durability in maintaining CR at landmark time points may be over-estimated due to limited follow-up. Based on FDA's analysis, the observed percentage of patients who maintained CR at 9 months is 42.9% (95% CI: 26.3, 60.6).

### 2.3.3 Supportive Phase 3 Study ATLAS Results

The Applicant's Position:

#### *2.3.3.1 Demographic and Baseline Disease Characteristics*

A total of 282 patients were randomized in ATLAS (142 in the UGN-102 arm and 140 in the TURBT arm), of whom 108 were included in the FDA Analysis Population (51 and 57, respectively). Demographic and baseline disease characteristics were generally well balanced across treatment groups. Median age was 69 (range, 45-85) years in the UGN-102 arm and 69 (range, 47-88) years in the TURBT arm. Most patients in both arms were male (72.5% in the UGN-102 arm and 64.9% in the TURBT arm). All patients in both arms were White, and most patients were not Hispanic or Latino (98.0% in the UGN-102 arm and 96.5% in the TURBT arm).

Among patients treated with UGN-102, 47 (92.2%) completed all 6 planned instillations. All patients in both treatment groups had a previous LG-NMIBC episode and a prior TURBT for LG-NMIBC. Other disease-related characteristics in the UGN-102 and TURBT arms, respectively, included ≥2 previous LG-NMIBC episodes (47.1% and 47.4%), previous LG-NMIBC episodes within 1 year of current diagnosis (64.7% and 59.6%), multiple tumors at baseline (69.4% and 71.2%), longest tumor diameter ≤3 cm (89.8% and 89.5%), and total tumor burden ≤3 cm (75.0% and 71.2%). A slightly higher percentage of patients were current or former smokers in the UGN-102 arm (54.9%, compared with 43.9% in the TURBT arm).

See Appendix 8 for a complete summary of demographics and baseline disease characteristics in ATLAS.

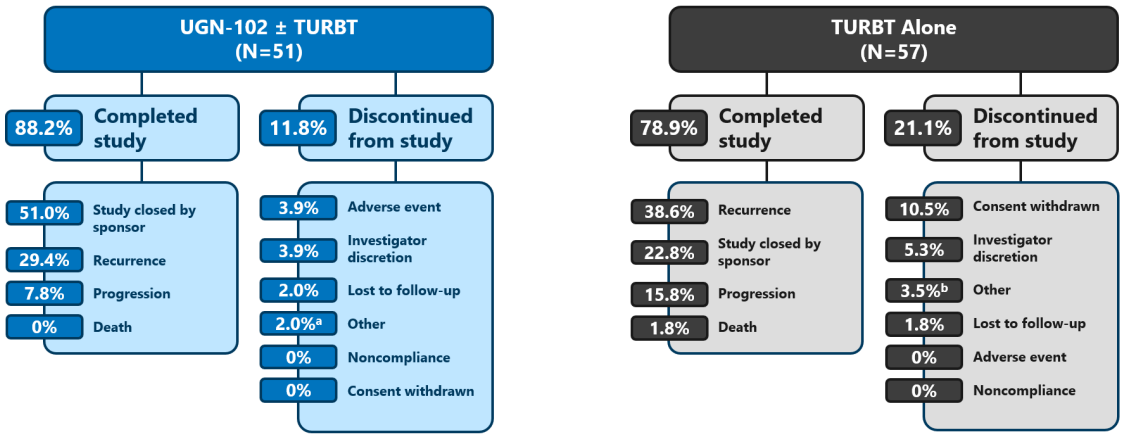
#### *2.3.3.2 Patient Disposition*

Because of the Sponsor's decision to close the study after the last patient reached the 15-month Visit, patients were considered to have completed the study if they remained in the study through the time of study closure by the Sponsor or if they had previously experienced disease recurrence, progression, or death.

Among randomized patients, 88.2% in the UGN-102 arm and 78.9% in the TURBT arm completed the study (Figure 10). The primary reason for study completion was study closure in the UGN-102 arm (51.0%) and disease recurrence (38.6%) in the TURBT arm.

Among patients who discontinued early from the study (11.8% in the UGN-102 arm and 21.1% in the TURBT arm), the main reasons were AE and investigator discretion (both 3.9%) in the UGN-102 arm and consent withdrawn (10.5%) and investigator discretion (5.3%) in the TURBT arm (Figure 10). AEs leading to treatment or study discontinuation were low are detailed in Section 3.

**Figure 10 Patient Disposition – FDA Analysis Population (ATLAS)**

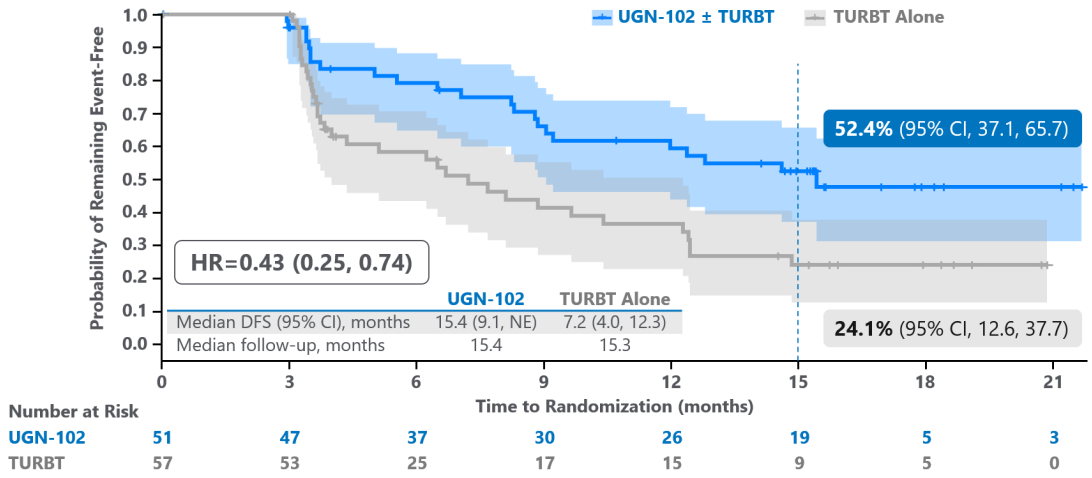



[a]"Other" reasons for discontinuation were "Sponsor required per protocol" in 1 patient.
[b]"Other" reasons for discontinuation were "post-TURBT histology was T1 process" in 1 patient, and "subject decision" in 1 patient.
TURBT=transurethral resection of bladder tumor.
Source Dataset: BL006-FDA Analysis Set-ADSL

#### *2.3.3.3 Primary Endpoint: Disease-Free Survival*

The prespecified primary DFS analysis is difficult to interpret because DFS was defined differently in each arm: residual disease at 3 months was counted as an event in the TURBT arm but not the UGN-102 arm (Section 2.2.3.1). Therefore, DFS was further examined using a sensitivity analysis that counted residual disease at 3 months as an event in both arms, which allowed comparison of UGN-102 alone versus TURBT. Median DFS was 15.4 months in the UGN-102 arm and 7.2 months in the TURBT arm. Treatment with UGN-102 reduced the risk of recurrence, progression, or death by 57% relative to TURBT (hazard ratio = 0.43; 95% CI: 0.25, 0.74) (Figure 11). At 15 months after randomization, the probability of remaining event free was 52.4% (95% CI: 37.1, 65.7) in the UGN-102 arm and 24.1% (95% CI: 12.6, 37.7) in the TURBT arm (Figure 11).

**Figure 11** **Disease-Free Survival Estimate – FDA Analysis Population (ATLAS, Sensitivity Analysis)**




Residual low-grade disease at 3 months is counted as an event in both arms.
CI=confidence interval; DFS=disease-free survival; HR=hazard ratio; NE=not estimable; TURBT=transurethral resection of bladder tumor.
Source: BL006-FDA Analysis Set-Table 14.2.1.9.1; Table 14.2.1.9.2; Figure 14.2.1.9.1

### *2.3.3.4 Secondary Endpoints: CRR at 3 Months, DOR, DCR Rate, Avoidance of TURBT*

The secondary endpoints CRR, DOR, and DCR measure the impact of the baseline interventions, UGN-102 versus TURBT. These endpoints are not affected by TURBTs done at 3 months for residual disease because CRR is measured prior to TURBTs done at 3 months for residual disease and because DOR and DCR are measured in the 3-month CR analysis set. These endpoints demonstrate the clinically meaningful efficacy of UGN-102 alone versus TURBT in patients with recurrent LG-IR-NMIBC, consistent with the results of ENVISION and OPTIMA II.

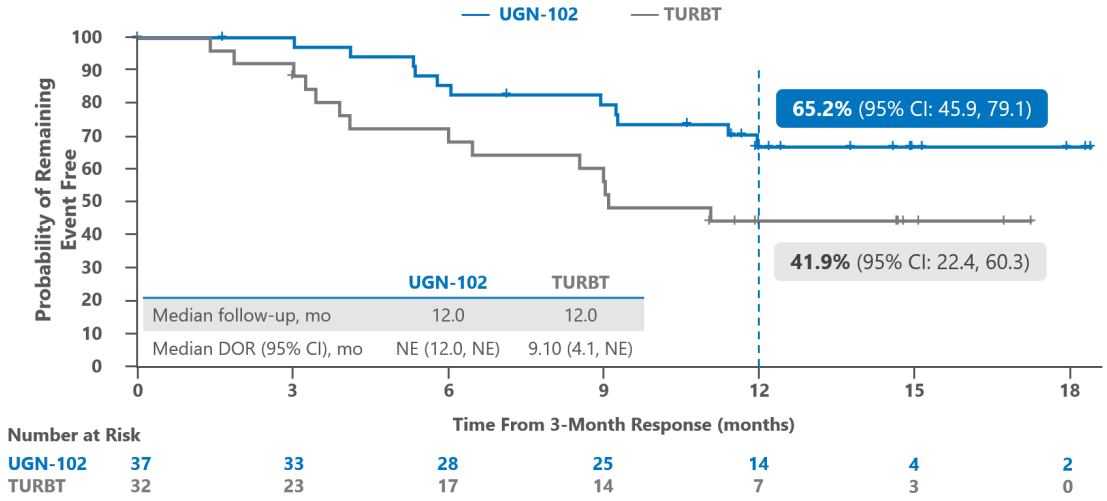
Of the patients in the FDA Analysis Population, the CRR at 3 months after the start of treatment was 72.5% (37 of 51) in the UGN-102 arm and 56.1% (32 of 57) in the TURBT arm. The CRR results demonstrate that chemoablation with UGN-102 achieved better disease eradication than TURBT in recurrent patients, without the need for an invasive surgical procedure under general anesthesia.

Among patients who achieved a CR at 3 months, treatment with UGN-102 improved DOR compared with TURBT alone. Median follow-up time for DOR was 12 months in both arms and median DOR was NE (95% CI: 12.0, NE) in the UGN-102 arm and 9.10 (95% CI: 4.1, NE) in the TURBT arm (Figure 12). The estimated probability of remaining in response at 12 months after 3-month CR by KM estimate was 65.2% (95% CI: 45.9, 79.1) for UGN-102 alone and 41.9% (95% CI: 22.4, 60.3) for TURBT alone (Figure 12).

In recurrent patients, the DCR rate 12 months after 3-month CR was meaningfully higher in the UGN-102 arm (56.8%; 95% CI: 39.5, 72.9) than in the TURBT arm (31.3%; 95% CI: 16.1, 50.0).

The clinical benefit for patients achieving a more durable CR with UGN-102 is a reduction in the burden of repeated TURBTs.

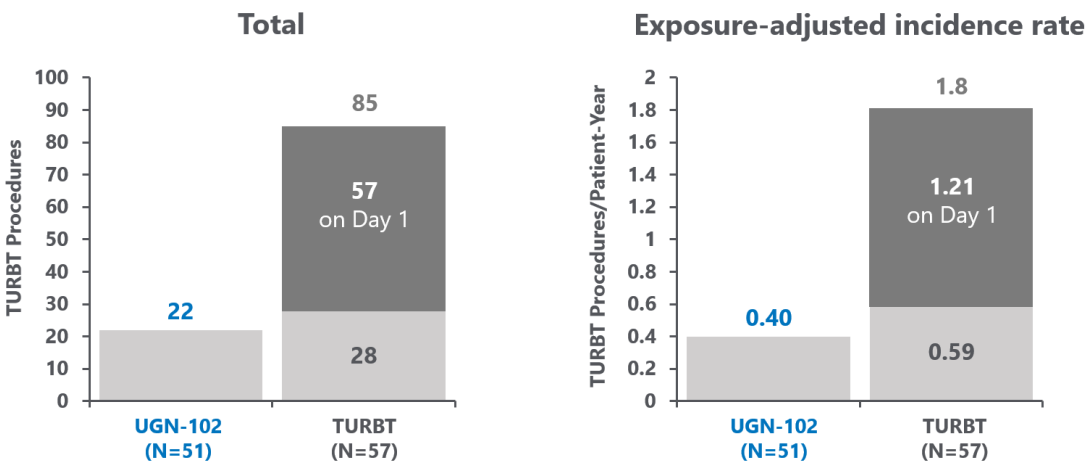
**Figure 12 UGN-102 Improved Duration of Response Compared With TURBT – FDA Analysis Population (ATLAS)**




CI=confidence interval; DOR=duration of response; NE=not estimable; TURBT=transurethral resection of bladder tumor.
Source: ISE-FDA Analysis Set- Table 14.2.2.1.1.1d; Table 14.2.2.1.2.1d; Dataset: ISE-FDA Analysis Set-ADTTE

Avoidance of TURBT was a prespecified secondary endpoint. Treatment with UGN-102 reduced the overall burden of TURBT in recurrent patients. During the study, a total of 22 TURBTs were performed during follow-up in the UGN-102 arm (Figure 13). In the TURBT arm, there were 85 TURBTs, with 57 performed at baseline and 28 during follow-up (Figure 13). Adjusting for exposure, the number of TURBTs per patient-year was 0.40 in the UGN-102 arm and 1.80 in the TURBT arm (Figure 13). Comparing only TURBTs performed during follow-up, the exposure-adjusted rates are 0.40 and 0.59, respectively (Figure 13). Reduction in the burden of TURBT under general anesthesia in this highly recurrent condition and generally elderly comorbid population is a highly meaningful outcome.

**Figure 13 UGN-102 Reduces the Overall Burden of TURBT – FDA Analysis Population (ATLAS)**




Dark gray indicates TURBTs performed at baseline. Light gray indicates TURBTs performed during Follow-up.
Exposure-adjusted incidence rate calculated as the number of TURBTs divided by the total patient study duration (years).
TURBT=transurethral resection of bladder tumor.
Source Dataset: BL006-FDA Analysis Set-ADSL; BL006-CSR-ADPR

The FDA's Position: The FDA agrees with the Applicant's description of the demographics, baseline disease characteristics, and patient disposition in the ATLAS trial as supportive evidence. The patient population enrolled included patients with both newly diagnosed and recurrent LG-IR-NMIBC, which differed from the population enrolled in the ENVISION trial (recurrent-only disease).

The FDA review team conducted exploratory analyses on data from ATLAS to assess CRR in a similar patient population as ENVISION. Among the 51 patients in the UGN-102 arm who had disease defined per ENVISION criteria (i.e., recurrent LG-IR-NMIBC), 37 patients had a CR at 3 months [72.5% (95% CI: 58.3, 84.1)]. While cross-trial comparisons are difficult to interpret due to bias, the CR rates in these exploratory analyses appear consistent with those from patients enrolled and treated with UGN-102 in ENVISION.

Per FDA's analysis, the percent of patients who maintained CR at 12 months was 40.5% (95% CI: 24.8, 57.9) for the UGN-102 arm and 21.9% (95% CI: 9.3, 40.0) for the TURBT alone arm, respectively. Note that these estimates should not be compared between treatment arms since these analyses are based on only patients who achieved CR and is not protected by randomization.

As the Applicant described, the pre-specified primary endpoint of DFS was problematic. The FDA considers this endpoint to be uninterpretable because of different definitions used in each arm and interpretability was limited due to early termination of the trial and short follow-up time.

Regarding the Applicant's sensitivity analysis of DFS, which applied a consistent definition across treatment arms, FDA notes that this analysis resulted in five additional events in the UGN-102 arm compared to the analysis based on the pre-specified DFS definition. Additionally, most DFS events appeared to reflect recurrence of low-grade disease rather than progression to high-grade disease — a pattern also observed with the pre-specified definition. Overall, due to the post-hoc modification of the DFS definition and the loss of randomization from including only recurrent patients, the DFS treatment effect observed in the Applicant's sensitivity analysis may be subject to bias. Therefore, FDA considers this analysis exploratory only.

For the secondary endpoint of TURBT avoidance, the Applicant states that treatment with UGN-102 reduced the overall burden of TURBT in recurrent patients. However, the FDA notes that of the 22 TURBTs performed during follow-up in the UGN-102 arm, 9 were performed at the 3-month assessments, and of the 28 TURBTs performed during follow-up in the TURBT arm, 15 were performed at the 3-month assessments. After the 3-month assessment, 13 TURBTs occurred in each arm, suggesting the observed difference in the number of TURBTs between arms may have been primarily attributed to the difference at the 3-month assessments. Also, the FDA reiterates that any comparison between arms should be interpreted with caution due to early trial termination and loss of randomization.

Regarding any comparative analyses between the UGN-102 arm and the TURBT alone arm in ATLAS, the FDA emphasizes that these data are difficult to draw conclusions from and should be interpreted with caution due to being conducted in non-randomized subgroups with no pre-specified planning. Furthermore, since the control arm is considered inferior, any cross-arm comparisons within the ATLAS study may be misleading.

### 2.3.4 Summary of Efficacy Across Trials

The Applicant's Position:

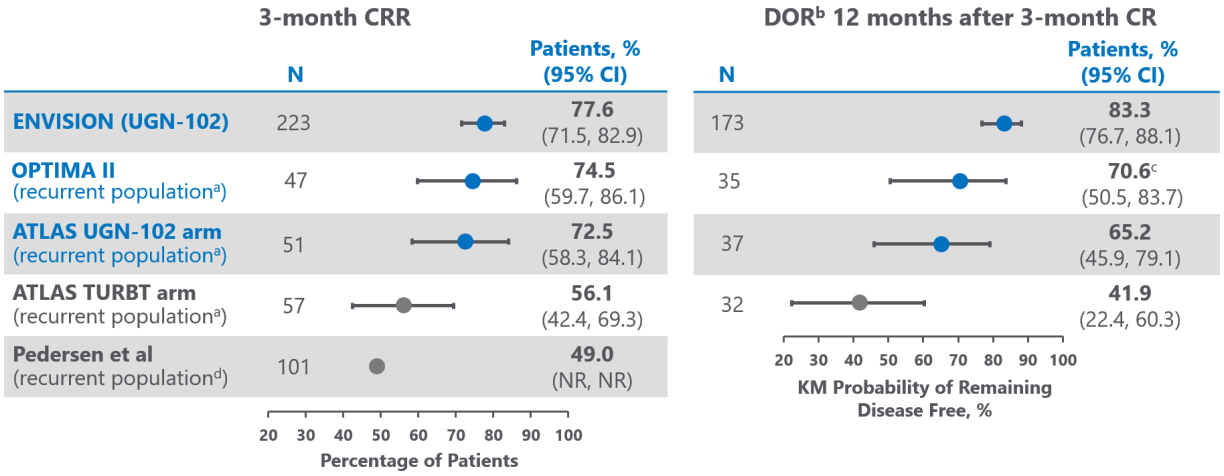
The CRR and 12-month DOR from ENVISION were compared with results from OPTIMA II and ATLAS, all conducted in recurrent patients (FDA Analysis Population). The larger sample size of ENVISION provides more precision in the measurement of these endpoints. The efficacy of UGN-102 in patients with recurrent LG-IR-NMIBC, as assessed by 3-month CRR and 12-month DOR, was consistent across the development program (Figure 14).

To put UGN-102 efficacy data into clinical context relative to current community-based care, the best comparison is with the TURBT arm in ATLAS. The inclusion and exclusion criteria and study procedures in the UGN-102 trials were the same (Appendix 4), and baseline characteristics were very similar (Sections 2.3.1.1, 2.3.2, and 2.3.3.1). The CRR and 12-month DOR achieved with UGN-102 were higher than with TURBT in ATLAS (Figure 14).

Finally, similar outcomes were observed between the TURBT arm of ATLAS and the findings in a contemporary trial that enrolled patients with recurrent IR-NMIBC, of whom 25% received

intravesical mitomycin following TURBT.[52] The 4-month recurrence-free survival reported in that study is similar to the 3-month CRR in the TURBT arm of ATLAS: ~50% (Figure 14).

**Figure 14 Complete Response Rate and Duration of Response With UGN-102 Were Consistent Across Trials and Better Than Standard of Care**




[a]FDA Analysis Population.
[b]KM estimate.
[c]9 months after 3-month CR.
[d]Recurrence-free survival at 4-months from Pedersen GL, et al. *Eur Urol*. 2023.[52]
CI=confidence interval; CR=complete response; CRR=complete response rate; DOR=duration of response; IR=intermediate risk; KM=Kaplan-Meier; LG=low grade; NMIBC=non-muscle invasive bladder cancer; NR=not reported; TURBT=transurethral resection of bladder tumor.
Source: ISE-FDA Analysis Set-Table 14.2.1.1.1a; Table 14.2.2.1.2.1d; BL011-M21-FDA Analysis Set-Table 14.2.2.2d

The FDA's Position:

The FDA considers the ENVISION trial to be the primary source of evidence for this application given the challenges in interpreting data from ATLAS and OPTIMA II as noted in other parts of this review. However, to further evaluate the reported CRR results from UGN-102 in the ENVISION trial, the FDA conducted post-hoc exploratory analyses, leveraging external data from the UGN-102 arm in the ATLAS trial to provide information on clinical outcomes in patients meeting eligibility criteria for ENVISION. The CR rates appeared consistent between the ENVISION trial and this exploratory analysis for patients receiving UGN-102. No other comparisons to data from OPTIMA II or ATLAS were made due to lack of interpretability.

### 2.3.5 Efficacy Conclusions

The Applicant's Position:

The efficacy of UGN-102 for the treatment of patients with recurrent LG-IR-NMIBC was established in the pivotal Phase 3 ENVISION trial, and results were consistent across the supportive trials OPTIMA II and ATLAS. In ENVISION, patients with recurrent LG-IR-NMIBC treated with UGN-102 achieved a clinically meaningful 77.6% CRR at 3 months that was durable through 18 months of follow-up (>80% probability of remaining event free 18 months after 3-month CR). Overall, efficacy results in the FDA Analysis Population are comparable to that in the ITT Analysis Population (Appendix 6). Prespecified subgroup analyses demonstrated that efficacy results were generally consistent across subgroups evaluated. The randomized Phase 3 ATLAS trial provides supportive evidence for the findings in ENVISION. The direct comparison of UGN-102 alone versus TURBT demonstrated an improved 3-month CRR and a meaningful improvement in DOR with UGN-102. Additionally, the DFS sensitivity analysis in ATLAS demonstrated that treatment with UGN-102 reduced the risk of recurrence, progression, or death by 57% relative to TURBT. Finally, the efficacy of UGN-102 in recurrent patients was consistent across trials. Importantly, UGN-102 is an alternative in-office treatment option that can reduce the burden of repeated TURBTs under general anesthesia in the elderly, comorbid, LG-IR-NMIBC population.

The FDA's Position: The FDA considers the reported CR rate in ENVISION (77.6%, 95% CI: 71.5, 82.9) to be interpretable and consistent with the CR rate in the subgroup analyses of patients with recurrent LG-IR-NMIBC from ATLAS (72.5%, 95% CI: 58.3, 84.1). Duration of response in ENVISION demonstrates that 79.2% of patients (95 % CI: 72.3, 85.0) maintain a CR at 12 months post-CR (i.e. 15 months from initial treatment). Due to limited follow up, ascertaining the number of patients who remain in response for longer time periods is confounded or unavailable. Additionally, subgroup analyses of the CR rate and duration of response based on whether patients had 1 or 2 protocol-specified risk factors for intermediate risk NMIBC were consistent with the overall population results in ENVISION.

Given the heterogeneity of the IR-NMIBC population, it must be considered that some patients may recur infrequently or never recur, while others may have frequent recurrences. The recurrence risk in this population has wide probabilities, with the natural history of the disease varying based on several known and unknown factors. The FDA thus considers a randomized trial the preferred design to demonstrate efficacy in this disease setting and the lack of a concurrent control in the single-arm ENVISION trial makes interpretation of efficacy challenging. The FDA does not agree with the Applicant's statement regarding direct comparison of UGN-102 vs TURBT; the FDA does not consider ATLAS appropriately designed to compare efficacy in the recurrent-only population given the loss of randomization when considering this exploratory subgroup as well as the issues regarding the non-inferiority design and primary endpoint definition. Further, treatment effects may be misleading as the control arm, which excluded post-operative chemotherapy instillation, did not reflect the most active standard of care.

Attaining a complete response to treatment of recurrent LG-IR-NMIBC would result in surveillance monitoring in clinical practice. If patients recurred in the future, they would be

candidates for further treatment depending on the type/stage of disease identified. Per guidelines, those with recurrent LG-IR-NMIBC would most likely undergo further TURBT with one post-operative instillation of intravesical chemotherapy.

A CR may be clinically meaningful if the duration of response is long, which may delay or obviate the need for further treatment, including repeat TURBTs. Thus, duration of response is a critical component of the efficacy evaluation. The single arm trial design of ENVISION does not allow for a robust evaluation of duration of response. Because there is no concurrent control, selection bias is possible, meaning that the population enrolled can have characteristics that may not represent the broader LG-IR-NMIBC population. The single arm trial design does not allow for distinguishing whether the observed duration of response in ENVISION is due to the investigational therapy, UGN-102, or the natural history of the disease. Assessing duration of response for this application requires comparison to historical (external) control, and as described above, recurrence probabilities are wide in this population and there is no well-established historical control.

Therefore, the Applicant's proposed utility of UGN-102 as a therapy that may "reduce the burden of repeated TURBTs under general anesthesia in the elderly, comorbid, LG-IR-NMIBC population" is unclear because of challenges in determining recurrence risk in this population.

# 3 Safety

## 3.1 Pharmacokinetics of UGN-102

The Applicant's Position:

Following local administration of UGN-102 into the bladder, there is minimal systemic absorption of mitomycin. The mean maximum plasma concentration ($C_{max}$) at the target dose of 75 mg was 2.3 ng/mL (range, 0.19-8.94 ng/mL), which is <1% of the expected $C_{max}$ after intravenous administration of mitomycin and <1% of the mitomycin plasma concentration associated with myelosuppression (400 ng/mL). At the highest dose tested, 120 mg, the mean $C_{max}$ was 20.4 ng/mL, well below the concentration associated with myelosuppression. Clinical pharmacology is summarized in more detail in Appendix 9.

The FDA's Position:

The FDA agrees with the Applicant's position regarding the observed exposure of mitomycin after intravesical administration of UGN-102. Myelosuppression has been observed at a range of mitomycin dosages and exposures when administered via other routes (i.e., intravenous, oral, intraperitoneal).

## 3.2 Overview of Safety Profile – Integrated Analysis (Pool 2)

The Applicant's Position:

### 3.2.1 Safety Datasets and Pooling Strategy

The primary data used to characterize the safety profile of UGN-102 are from the 4 late-phase clinical studies in adult patients with LG-IR-NMIBC (ENVISION, OPTIMA II, ATLAS, and the home instillation study), referred to as Pool 2. All 4 of these studies were conducted with the target UGN-102 dosing regimen (75 mg mitomycin instilled once weekly for 6 weeks into the bladder via a urinary catheter). The safety analysis set consists of all patients who received at least 1 intravesical instillation of UGN-102 preparation or received at least 1 TURBT intervention in the TURBT-alone arm of ATLAS. Safety data from the ENVISION trial are through a DCO date of April 4, 2024, which includes a minimum of 12 months (up to 18 months) of follow-up after the 3-month Visit. An overview of the safety profile in ATLAS is presented in Appendix 10.

### 3.2.2 Extent of Exposure

Safety data are based on a total of 449 patients exposed to UGN-102 for up to 6 weekly intravesical instillations (Pool 2). Of those, 423 patients (94.2%) received all 6 planned instillations, and >97% received at least 5 instillations.

### 3.2.3 Treatment-Emergent Adverse Events

UGN-102 demonstrated an acceptable and manageable safety profile that was as-expected given the intravesical route of administration, with TEAEs mainly localized to the lower urinary tract. Overall, 68.2% of patients in Pool 2 had treatment-emergent AEs (TEAEs) (Table 3). The majority of TEAEs (61.0%) occurred in the time period up to 3 months compared with 35.9% in the time period post 3 months (Table 3). Across all time periods, the majority of TEAEs were Grade 1-2 with low rates of TEAEs leading to treatment or study discontinuation (Table 3). Additionally, serious TEAEs occurred at low rates across all time periods, with very few that were treatment or procedure related (i.e., related to catheter insertion, cystoscopy, or biopsy). Treatment-related serious TEAEs occurred in 2 patients (urethral stenosis and urinary retention in 1 patient each) and both resolved (Table 3). TEAEs leading to death occurred in 4 patients (0.9%) overall in Pool 2 and were cardiac failure, cardiac disorder, pneumonia, and death (Table 3). None of the deaths were considered related to study treatment or study procedures. TEAEs of special interest (referred to here as AEs of special interest [AESIs]) occurred in 51.7% of patients in Pool 2, with most of these events occurring in the first 3 months (Table 3).

AESIs and AEs leading to death in Pool 2 are discussed in more detail in Sections 3.4 and 3.5, respectively.

**Table 3 Overall Summary of Adverse Events (Pool 2)**

| | Overall (N=449) n (%) | Up to 3 Months (N=449) n (%) | Post 3 Months (N=409) n (%) |
|---|---|---|---|
| **TEAEs** | **306 (68.2)** | **274 (61.0)** | **147 (35.9)** |
| Treatment-related | 176 (39.2) | 174 (38.8) | 15 (3.7) |
| Procedure-related | 131 (29.2) | 122 (27.2) | 27 (6.6) |
| TEAEs leading to treatment discontinuation | 19 (4.2) | 19 (4.2) | 0 |
| TEAEs leading to study discontinuation | 13 (2.9) | 7 (1.6) | 6 (1.5) |

| | | | |
|---|---|---|---|
| Grade 3 or higher TEAEs | 52 (11.6) | 26 (5.8) | 27 (6.6) |
| Serious TEAEs | 49 (10.9) | 25 (5.6) | 26 (6.4) |
| Treatment related[a] | 2 (0.4) | 2 (0.4) | 0 |
| Procedure related | 5 (1.1) | 4 (0.9) | 1 (0.2) |
| TEAEs leading to death[b] | 4 (0.9) | 1 (0.2) | 3 (0.7) |
| TEAEs of special interest | 232 (51.7) | 213 (47.4) | 66 (16.1) |

[a]Treatment-related serious TEAEs occurred in 2 patients in the UGN-102 arm (urethral stenosis and urinary retention) and both resolved.
[b]Four deaths occurred in the UGN-102 arm (cardiac disorder, death, pneumonia, and cardiac failure). No deaths were considered related to study treatment or procedure.
TEAE=treatment-emergent adverse event.
Source: ISS-Table 14.3.1.1.1

### 3.2.4 Most Commonly Reported Adverse Events

The most common individual TEAEs (occurring in >5% of patients) in Pool 2 were localized to the lower urinary tract (with the exception of fatigue), were mostly low-grade (Grade 1 or 2), and were manageable as part of standard urological practice. For the overall study duration, the incidence of TEAEs was highest in the system organ class (SOC) of Renal and Urinary Disorders (46.3%). The most common TEAEs by Preferred Term (PT) for the overall study duration in Pool 2 were dysuria (27.6%), pollakiuria (11.6%), micturition urgency (9.6%), hematuria (8.9%), nocturia (7.3%), urinary tract infection (7.1%), and fatigue (6.0%) (Table 4).

**Table 4 Common TEAEs Were Mostly Low Grade and Localized to Urinary Tract (Pool 2)**

| | **Overall (N=449) n (%)** | |
|---|---|---|
| **Preferred Term[a]** | **All Grades** | **Grade ≥3** |
| **Patients with any TEAE** | **306 (68.2)** | **52 (11.6)** |
| Dysuria | 124 (27.6) | 1 (0.2) |
| Pollakiuria | 52 (11.6) | 0 |
| Micturition urgency | 43 (9.6) | 0 |
| Hematuria | 40 (8.9) | 1 (0.2) |
| Nocturia | 33 (7.3) | 0 |
| Urinary tract infection | 32 (7.1) | 1 (0.2) |
| Fatigue | 27 (6.0) | 0 |

[a]TEAEs (all grades) reported in >5% of patients in Pool 2.
AESI=adverse event of special interest; TEAE=treatment-emergent adverse event.
Source: ISS-Table 14.3.1.3.1; Table 14.3.1.7.2

### 3.2.5 TEAEs Leading to Treatment or Study Discontinuation

In Pool 2, 19 patients (4.2%) discontinued UGN-102 treatment due to TEAEs. Events in the SOC of Renal and Urinary Disorders were the most common TEAEs leading to treatment discontinuation (10 patients, 2.2%). Nine patients (2.0%) discontinued treatment due to TEAEs that were considered related to UGN-102. Six of these 9 patients discontinued due to events in the Renal and Urinary Disorders SOC, including dysuria (3 patients), lower urinary tract symptoms (2 patients), and micturition urgency, nocturia, urinary retention, and urge

incontinence (1 patient each). Other TEAEs leading to treatment discontinuation considered related to UGN-102 were hand dermatitis, penile erythema, rash, and hypersensitivity (1 patient each). TEAEs leading to treatment discontinuation in Pool 2 were Grade 1 or 2 except for 1 TEAE of Grade 3 dysuria; all resolved. See Appendix 11 for a summary of TEAEs leading to treatment discontinuation in Pool 2.

Thirteen patients (2.9%) in Pool 2 discontinued the study due to TEAEs. No TEAE leading to study discontinuation was reported in more than 1 patient. By SOC, the most frequently reported (≥2 patients) TEAEs leading to study discontinuation were Neoplasms in 4 patients (0.9%), Nervous System Disorders in 3 patients (0.7%), and Renal and Urinary Disorders in 2 patients (0.4%). One patient discontinued the study due to a TEAE considered related to UGN-102, which was Grade 1 dysuria that occurred in the first 3 months and resolved.

### 3.2.6 Serious Adverse Events

Serious TEAEs were reported across multiple SOCs. Two patients had treatment-related serious TEAEs (urethral stenosis and urinary retention in 1 patient each) and both resolved (Table 3).

The most frequently occurring serious AEs (SAEs) by PT are shown in Table 5. For the overall study duration, serious TEAEs occurred in 10.9% of patients in Pool 2, most frequently in the SOCs of Infections and Infestations (2.7%) and Cardiac Disorders (2.2%) (Table 5). Serious TEAEs in the SOC of Renal and Urinary Disorders occurred in 1.3% of patients (Table 5). The incidence of serious TEAEs was similar up to 3 months (5.6%) and post 3 months (6.4%).

Five patients (1.1%) had procedure-related serious TEAEs in the SOCs of Renal and Urinary Disorders or Infections and Infestations. The events were urethral stenosis (2 patients) and urinary retention, urosepsis, and Fournier's gangrene (1 patient each). All procedure-related serious TEAEs occurred in the first 3 months except for 1 event of urethral stenosis (onset Study Day 365) and resolved.

In Pool 2, the similar incidence of serious TEAEs in the first 3 months versus post 3 months, and the fact that most of these events were considered not related to study treatment or procedures, suggests that serious TEAEs in these studies were most likely associated with comorbidities in the patient population and not caused by UGN-102.

**Table 5 Serious TEAEs in 2 or More Patients in the Overall Study Period (Pool 2)**

| **System Organ Class**<br>Preferred Term | **UGN-102 Pool 2 (N=449) n (%)** |
|---|---|
| Patients with any serious TEAE | 49 (10.9) |
| **Infections and Infestations** | 12 (2.7) |
| COVID-19 | 6 (1.3) |
| Pneumonia | 3 (0.7) |
| **Cardiac Disorders** | 10 (2.2) |
| Atrial fibrillation | 3 (0.7) |
| **Neoplasms Benign, Malignant, Unspecified** | 7 (1.6) |

| | |
|---|---|
| **Nervous System Disorders** | 6 (1.3) |
| Cerebrovascular accident | 2 (0.4) |
| **Renal and Urinary Disorders** | 6 (1.3) |
| Urinary retention | 3 (0.7) |
| Urethral stenosis | 2 (0.4) |
| **Respiratory, Thoracic and Mediastinal Disorders** | 5 (1.1) |
| Chronic obstructive pulmonary disease | 2 (0.4) |
| **Gastrointestinal Disorders** | 3 (0.7) |
| **Injury, Poisoning, and Procedural Complications** | 3 (0.7) |
| **Hepatobiliary Disorders** | 2 (0.4) |

COVID-19=coronavirus disease 2019; TEAE=treatment-emergent adverse event.
Source: ISS-Table 14.3.2.1

The FDA's Position: The Applicant cites treatment emergent adverse events (TEAEs) that were attributed to study treatment and/or study procedures. The FDA review considers all TEAEs regardless of attribution due to the difficulty and subjectivity associated with determining attribution of adverse events. This resulted in differences calculated between the Applicant and the FDA with respect to incidence rates of some adverse events. Additional differences are likely due to differences in how similar adverse events were grouped together, but these differences are unlikely to affect interpretation of safety. The FDA notes any differences that might be relevant where applicable.

Adverse events primarily affected the genitourinary tract, which is expected given the intravesical administration of the investigational product. Patients receiving UGN-102 may be at risk for urethral stenosis, which occurred in 4.5% of patients, potentially due to repeated catheterization. The FDA agrees that most adverse events were Grade 1-2 in severity.

The FDA analysis of urinary tract infections included multiple related terms (e.g. cystitis and pyelonephritis) resulting in an incidence of 10.5%. The FDA agrees with the incidence rate of TEAEs leading to treatment discontinuation, but also notes that 10% of patients had TEAEs leading to an interruption in treatment. Further, the FDA disagrees with the statement that there was only one Grade 3 event that lead to treatment discontinuation. FDA analysis identified 7 patients with Grade 3-4 (only one Grade 4 event) TEAEs that led to treatment discontinuation, including one patient who discontinued therapy after a Grade 3 event of urosepsis. The FDA acknowledges, with the exception of the Grade 3 events of dysuria and urosepsis, the other Grade 3-4 events that led to treatment discontinuation were unlikely related to investigational therapy.

Due to the single-arm design of ENVISION and limited follow up in ATLAS, events that may have been due to repeat TURBT procedures (e.g., anesthesia-related complications, cardiopulmonary risk, overall mortality) were not adequately captured in the safety database.

Due to lack of a control arm in ENVISION (and the other single-arm trials included in Pool 2) it is difficult to put the observed toxicity into context. ATLAS, while terminated early, provides comparative safety data between patients receiving TURBT +/- UGN-102 vs. TURBT alone, with the challenge to interpretation being that safety assessments were conducted at different

intervals between arms in ATLAS.

Patients receiving UGN-102 in ATLAS reported higher rates of genitourinary toxicity, including events such as dysuria (30% vs 4.5%), increased urinary frequency (19% vs 8%), nocturia (18% vs 7%), hematuria (7% vs 4.5%), erectile dysfunction (7% vs 3%), and malaise (6% vs 1.5%) compared to patients undergoing TURBT alone. However, the comparison between arms may be confounded by an ascertainment bias due to differences in the collection of adverse events between arms. Patients in the UGN-102 arm had adverse event collection at screening, then weekly for 6 weeks while receiving therapy and again at months 2, and 3. Patients in the TURBT alone arm only had adverse event collection scheduled at screening, day 1 of surgery, and at months 1, 2, and 3.

## 3.3 Overview of Safety Profile – ENVISION

The Applicant's Position:

Overall, 57.1% of patients experienced TEAEs in ENVISION (DCO date April 4, 2024). TEAEs occurred in 49.6% of patients in the time period up to 3 months and in 31.9% of patients in the time period post 3 months (Table 6). Overall, treatment- or procedure-related TEAEs occurred in 40.4% of patients, most (39.2%) reported in the first 3 months (7.7% reported post 3 months) (Table 6).

Overall, serious TEAEs occurred in 12.1% of patients and were evenly spread across the time periods (Table 6). Treatment-related serious TEAEs occurred in 2 patients, and procedure-related serious TEAEs occurred in 3 patients; all were in the first 3 months (Table 6).

TEAEs leading to treatment discontinuation occurred in 2.9% of patients (Table 6). TEAEs leading to study discontinuation occurred in 2.5% of patients; none were related to study treatment or procedures (Table 6).

Three deaths occurred during the study, 1 in the first 3 months (cardiac failure) and 2 post 3 months (pneumonia and death); none were considered related to study treatment (Table 6). These deaths in ENVISION are also presented as a part of the deaths in Pool 2 (Table 8).

Overall, AESIs were reported in 41.7% of patients, with the majority (37.9%) occurring in the first 3 months and 13.6% post 3 months (Table 6).

**Table 6 Overall Summary of Adverse Events (ENVISION)**

| | Overall | Up to 3 Months | Post 3 Months |
|---|---|---|---|
| | UGN-102 (N=240) n (%) | UGN-102 (N=240) n (%) | UGN-102 (N=235) n (%) |
| AEs | 140 (58.3) | 119 (49.6) | 75 (31.9) |
| SAEs | 30 (12.5) | 14 (5.8) | 16 (6.8) |
| TEAEs | 137 (57.1) | 119 (49.6) | 75 (31.9) |
| Grade ≥3 TEAEs | 33 (13.8) | 15 (6.3) | 19 (8.1) |

| | Overall | Up to 3 Months | Post 3 Months |
|---|---|---|---|
| | UGN-102 (N=240) n (%) | UGN-102 (N=240) n (%) | UGN-102 (N=235) n (%) |
| Treatment- or procedure-related TEAEs | 97 (40.4) | 94 (39.2) | 18 (7.7) |
| Treatment-related TEAEs | 81 (33.8) | 80 (33.3) | 9 (3.8) |
| Procedure-related TEAEs | 64 (26.7) | 58 (24.2) | 17 (7.2) |
| TEAEs leading to treatment discontinuation | 7 (2.9)[a] | 7 (2.9)[a] | 0 |
| TEAEs leading to study discontinuation | 6 (2.5) | 2 (0.8) | 4 (1.7) |
| Serious TEAEs | 29 (12.1) | 14 (5.8) | 16 (6.8) |
| Treatment- or procedure-related serious TEAEs | 4 (1.7) | 4 (1.7) | 0 |
| Treatment-related serious TEAEs | 2 (0.8) | 2 (0.8) | 0 |
| Procedure-related serious TEAEs | 3 (1.3) | 3 (1.3) | 0 |
| TEAEs leading to death | 3 (1.3) | 1 (0.4) | 2 (0.9) |
| AESIs | 100 (41.7) | 91 (37.9) | 32 (13.6) |

[a]In addition to the patients shown here, 2 had TEAEs leading to UGN-102 treatment interruption and did not resume treatment. Because the events were categorized as treatment interruptions, these patients are not counted in summary tables as having TEAEs leading to treatment discontinuation.
AE=adverse event; AESI=adverse event of special interest; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Source: BL011-CSR-Table 14.3.1.1

The FDA's Position: The FDA agrees with the Applicant's position. However, see Section 3.2 above for additional details. Regarding the TEAEs that led to treatment discontinuation, while not explicitly discussed above by the Applicant, the FDA notes that four patients discontinued therapy due to lower urinary tract symptoms, one patient discontinued for urosepsis, and one patient discontinued therapy for a Grade 2 hypersensitivity reaction. The FDA review team considers these events to be likely related to the study treatment.

## 3.4 Adverse Events of Special Interest

The Applicant's Position:

AESIs were selected to evaluate potential local effects of UGN-102 instillation in the bladder (i.e., lower urinary tract symptoms, voiding interruption due to urethral/penile edema [unrelated to prostatic hypertrophy], and genitourinary infections) based on observations in early-phase clinical studies and to evaluate potential risks associated with the use of any chemotherapeutic agent (i.e., allergic reactions and bone marrow suppression). The designation of an event as an AESI does not necessarily indicate a causal relationship to study treatment.

AESIs were identified through manual clinical/safety review of all AEs by SOC and PT prior to database lock. The 5 categories of AESIs are lower urinary tract symptoms (LUTS), voiding interruption due to urethral/penile edema (unrelated to prostatic hypertrophy), genitourinary infections, allergic reactions, and bone marrow suppression.

Overall, 51.7% of patients in Pool 2 had an AESI (Table 7). Treatment- or procedure-related AESIs occurred in 42.3% of patients in Pool 2 (35.9% treatment related, 26.1% procedure related) (Table 7).

AESIs were reported more frequently in the time period up to 3 months (47.4%) than in the time period post 3 months (16.1%).

Overall, most patients with AESIs had events that were Grade 1 or 2 in severity. There were 12 patients (2.7%) in Pool 2 who had Grade 3 events, and there were no Grade 4 or 5 AESIs. AESIs were serious in 7 patients (1.6%) in Pool 2 (0.4% treatment related and 1.1% procedure related) (Table 7). AESIs led to treatment discontinuation in 14 patients (3.1%) in Pool 2 (2.0% treatment related and 1.6% procedure related) and to study discontinuation in 1 patient (0.2%) in Pool 2 (PT dysuria).

**Lower urinary tract symptoms (LUTS):** AESIs of LUTS occurred in 39.6% of patients in Pool 2 (Table 7). The most common individual TEAEs were dysuria, pollakiuria, micturition urgency, and nocturia. Among patients with an AESI of LUTS, the median time to onset was 17 days and tended to be of limited duration with a median of 8 days for the first event.

**Voiding interruption due to urethral/penile edema:** AESIs in this category occurred with an overall incidence of 10.9% in Pool 2, most commonly due to urinary retention or urethral stenosis (Table 7).

**Genitourinary infections:** AESIs in this category occurred with an overall incidence of 12.7% in Pool 2, most commonly due to urinary tract infection (Table 7).

**Allergic reactions:** AESIs in this category occurred with an overall incidence of 11.1% in Pool 2 (Table 7). The most common individual TEAEs in this category were rash, pruritus, and pruritus genital.

**Bone marrow suppression:** AESIs in this category occurred in 2.4% of patients in Pool 2 (Table 7). No events in this category led to discontinuation of UGN-102. Combined with the laboratory data showing similarly few patients with post-baseline worsening of hematology parameters to Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥3 (≤0.7% for any given parameter in Pool 2), these data indicate that UGN-102 is not associated with a clinically meaningful risk of bone marrow suppression.

**Table 7 Overall Summary of AESIs by Category**

| | **UGN-102 Pool 2 (N=449) n (%)** |
|---|---|
| **Patients with AESIs** | 232 (51.7) |
| **Patients with treatment- or procedure-related AESIs** | 190 (42.3) |
| **Patients with treatment-related AESIs** | 161 (35.9) |
| **Patients with procedure-related AESIs** | 117 (26.1) |

| | UGN-102 Pool 2 (N=449) n (%) |
|---|---|
| **Patients with serious AESIs** | 7 (1.6) |
| **Worst severity** | |
| Severe or medically significant | 12 (2.7) |
| Life-threatening consequences | 0 |
| Death related to AE | 0 |
| **Worst action taken** | |
| Drug permanently discontinued | 14 (3.1) |
| Drug temporarily withheld | 25 (5.6) |
| **Categories of AESIs** | |
| Lower urinary tract symptoms | 178 (39.6) |
| Voiding interruption due to urethral/penile edema | 49 (10.9) |
| Genitourinary infections | 57 (12.7) |
| Allergic reactions | 50 (11.1) |
| Bone marrow suppression | 11 (2.4) |

AE=adverse event; AESI=adverse event of special interest.
Source: ISS-Table 14.3.3.2

The FDA's Position: The FDA agrees with the Applicant's position. Serious AESIs were rare, but as shown above in Table 7, genitourinary symptoms were common, and these symptoms may develop/persist throughout the 6-week treatment course. See Section 3.2 for further details.

## 3.5 Adverse Events Leading to Death (Pool 2)

The Applicant's Position:

Four deaths (0.9%) were recorded in the safety database as of the April 4, 2024, DCO date in Pool 2 (Table 8). None of the deaths were considered related to study treatment. Three deaths occurred in the post 3 months period (exacerbation of chronic heart disease, pneumonia, and death), and 1 death occurred in the up to 3 months period (cardiac failure) (Table 8).

**Table 8 Deaths in UGN-102 Treated Patients (Pool 2)**

| Study Arm | Age (years)/Sex | Event Leading to Death | Study Day of Event Onset | Study Day of Death | Relationship to Study Treatment |
|---|---|---|---|---|---|
| Pool 2 | 91/M | Exacerbation of chronic heart disease (PT cardiac disorder) | 137 | 149 | Not related |
| Pool 2 | 69/M | Death | After Day 185 | After Day 185 | Not related |
| Pool 2 | 81/M | Pneumonia | 120 | 128 | Not related |
| Pool 2 | 74/F | Cardiac failure | 50 | 50 | Not related |

PT=preferred term.
Source: ISS-Listing 16.2.3.1; Listing 16.2.3.4.

The FDA's Position: The deaths observed were unlikely related to the investigational therapy. However, regarding the event of cardiac failure, this event occurred 14 days after the patient's

last dosage of UGN-102, and therefore the contribution of UGN-102 cannot be definitively ruled out, although we also acknowledge the patient had a history of cardiac disease that could provide a more likely alternative etiology. Notably, in ATLAS, no deaths appeared to be related to undergoing TURBT and associated general anesthesia.

## 3.6 Summary of Clinical Laboratory Evaluations (Pool 2)

There was no evidence of a clinically significant adverse impact of UGN-102 on laboratory results. Additionally, worsening of hematology or clinical chemistry parameters to CTCAE Grade ≥3 was infrequent. A detailed discussion of clinical laboratory evaluations, vital signs, and physical examination findings is presented in Appendix 12.

The FDA's Position: The FDA agrees that Grade ≥3 laboratory abnormalities were infrequent. However, the FDA analysis found that 20.1% (26.4% per Applicant analysis) of patients had an increase of at least one grade in creatinine from baseline and while the clinical significance of such renal impairment is unclear, mild elevations in creatinine have been associated with long-term complications, such as chronic kidney disease.

## 3.7 Safety Conclusions

The Applicant's Position:

The safety profile of UGN-102 is acceptable and manageable as part of standard urological practice. As expected, TEAEs were mainly localized to the lower urinary tract, consistent with intravesical chemotherapy. These localized lower urinary tract symptoms mostly occurred in the first 3 months and were of limited duration. The rates of TEAEs leading to treatment or study discontinuation were low, as was the frequency of Grade ≥3 TEAEs and SAEs in the Renal and Urinary Disorders SOC.

The majority of AESIs were low grade in severity and occurred mainly in the first 3 months. The most frequently occurring AESI category was LUTS. Importantly, treatment with UGN-102 results in minimal systemic absorption of mitomycin and is associated with a low risk of systemic side effects, with no clinically meaningful risk of bone marrow suppression.

The FDA's Position:

As discussed in Section 3.2, the FDA agrees that most adverse events observed in trials evaluating UGN-102 were low-grade (Grades 1-2), reversible, and involved the genitourinary tract. However, many patients experienced adverse events throughout and after the 6-week treatment period. The safety of administering UGN-102 for 6 weeks consecutively should be considered in the context of the current available standard of care, TURBT +/- a single instillation of intravesical chemotherapy. Patients undergoing TURBT may have toxicity, primarily genitourinary in nature, however, this would be expected to be shorter in duration given the single procedure. In ATLAS, comparison between arms is challenging due to differences in adverse event reporting, however the trial does not provide evidence that UGN-102 is safer or more tolerable than TURBT.

# 4 Clinical Outcome Assessment Analyses

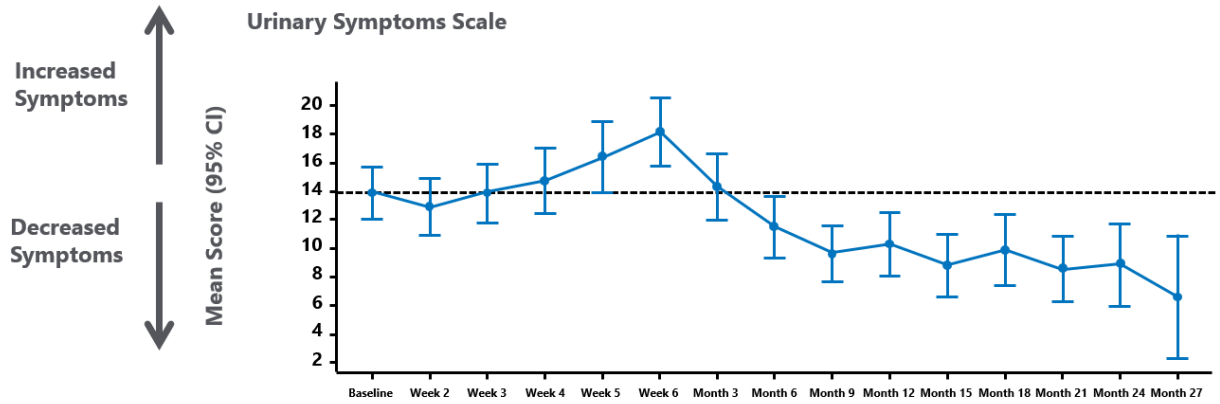
## 4.1 Health-Related Quality of Life and Patient Preference

The Applicant's Position:

Health-related QoL was assessed using the EORTC Quality of Life Questionnaire for Cancer Patients (QLQ-C30) in ENVISION and the EORTC Quality of Life Questionnaire for Non-Muscle-Invasive Bladder Cancer (QLQ-NMIBC24) in ENVISION, OPTIMA II, and ATLAS. In ENVISION, both the EORTC QLQ-NMIBC24 and QLQ-C30 scales/items assessed were completed by at least 94.1% of the expected number of patients at all planned assessments. PRO completion rates were not calculated for OPTIMA II because of missed and delayed assessments caused by the COVID-19 pandemic. In ATLAS, the EORTC QLQ-NMIBC24 scales/items assessed were completed by at least 90.0% of the expected number of patients at all planned assessments except for Week 1, which had a completion rate of 88.4%.

At baseline, patients generally had a high level of physical functioning and a low symptom burden, supporting that maintenance of PRO scores during and after treatment would be a favorable outcome. Results from the QLQ-C30 and QLQ-NMIBC24 demonstrated that patients did not perceive treatment with UGN-102 to adversely affect their symptoms, functioning, or QoL. Lower urinary tract symptoms were the most commonly reported AEs in the UGN-102 development program (Section 3.2.4). Figure 15 depicts mean scores for the QLQ-NMIBC24 urinary symptoms scale, with lower scores representing decreased symptom burden. In ENVISION, UGN-102 treatment was associated with a transient worsening of urinary symptoms from baseline to Week 6 that did not reach the minimal clinically important difference (MCID), followed by a return to baseline by Month 3 (Figure 15). Changes from baseline were not clinically meaningful for any of the other scales or individual items of the QLQ-C30 and the QLQ-NMIBC24 (completed by >5 patients). See Appendix 13 for further discussion of the PROs.

**Figure 15 Patient Reported Outcomes Indicate UGN-102 Did Not Adversely Affect Quality of Life (ENVISION)**




| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PRO Completed (n) | 239 | 231 | 232 | 227 | 225 | 233 | 225 | 182 | 167 | 158 | 146 | 143 | 134 | 74 | 26 |
| PRO Not Completed (n) | 1 | 8 | 6 | 11 | 13 | 5 | 10 | 1 | 1 | 3 | 2 | 3 | 6 | 3 | 4 |
| PRO Expected (n) | 240 | 239 | 238 | 238 | 238 | 238 | 235 | 183 | 168 | 161 | 148 | 146 | 140 | 77 | 30 |

PROs are derived from the Safety Analysis Set.
CI=confidence interval; PRO=patient-reported outcome.
Source: BL011-M21-ePRO-Figure 14.2.6.2.3

Qualitative patient interviews conducted in ENVISION demonstrated a clear patient preference for UGN-102 over TURBT. Of 39 eligible US patients, 31 completed baseline interviews at screening about their experience with prior TURBT procedures, 32 completed interviews at the 3-month Visit about treatment with UGN-102, and 29 completed both. Patients reported that while they generally considered a TURBT procedure to be the "gold standard" for bladder cancer treatment, there were multiple challenges during and after every surgery. At the follow-up interview at 3 months, patients described concerns with TURBT that included bleeding, being anesthetized, and catheter issues that were worse and longer lasting than with UGN-102. Patients reported that UGN-102 had less of an impact on their daily activities and responsibilities (e.g., work, recreation and exercise, sexual activity), and 90% stated that they would recommend UGN-102, which was perceived to be less invasive, less painful, and less time-consuming than TURBT. Despite the small sample size, there was strong agreement among patients and consistency in their responses.

The FDA's Position:

The EORTC Quality of Life Questionnaire for Cancer Patients (QLQ-C30) and the EORTC Quality of Life Questionnaire for Non-Muscle-Invasive Bladder Cancer (QLQ-NMIBC24) patient reported outcomes (PROs) were exploratory in the ENVISION and ATLAS trials and should be interpreted with caution due to significant limitations, including concerns with the adequacy of study designs to measure PROs:

1) Incomplete PRO assessment strategy: The PRO assessment frequency did not fully capture timepoints of treatment side effects. There were no PRO data collected between the last treatment installment (week 6) and the beginning of the follow-up period / disease assessment visit (month 3). The FDA notes that in the first 6 weeks, urinary symptoms are worsening, however, no PROs were collected to assess the peak and trajectory of these side effects after the last treatment installment, obscuring the full picture of safety and tolerability for UGN-102. Additionally, ATLAS PRO assessment frequency was asynchronous between the UGN-102 and control arms. Interpretation is difficult with limited data since only the assessment at the 3-month visit allows comparison across arms. Lastly, overall side effect impact was not assessed, which could have provided additional detail regarding tolerability and the cumulative burden of urinary symptoms.

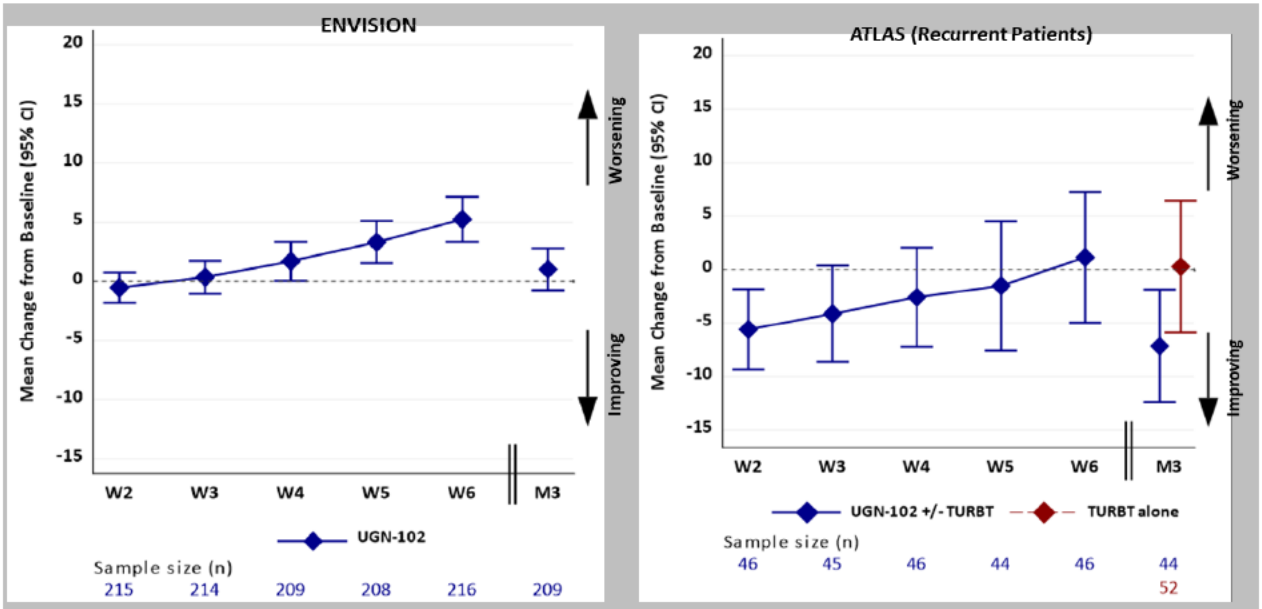
2) Potential selection bias due to PRO collection: In the follow-up period of ENVISION, QLQ-C30 and QLQ-NMIBC24 were administered only to patients who achieved complete response at the 3-month visit. In the follow-up period of ATLAS, patients from both arms without complete response at the 3-month visit may receive TURBT and subsequently complete PRO assessments. These selected subsets of trial participants introduce uncertainty and unreliability on the overall safety and tolerability profile of UGN-102.

Given these above limitations, the FDA performed PRO analyses on the urinary symptoms scale from QLQ-NMIBC24 during treatment period and at the first follow-up visit (month 3).

The FDA's Figure 1 below shows mean change from baseline for urinary symptom scale in QLQ-NMIBC24 while on-treatment and the first follow-up visit for both the ENVISION and ATLAS trials. In both the ENVISION and ATLAS trials, patients treated with UGN-102 exhibited progressively worsening urinary symptoms during the 6-week course of UGN-102, however the peak and trajectory of resolution were not captured. In both trials, it is unclear what urinary symptoms would be at these timepoints in patients not treated with UGN-102 as in both trials there was no contemporaneous assessment of symptoms. The difference between arms in the ATLAS trial at month 3 appears negligible and the interpretation of these results are hampered by the small sample size.

The FDA disagrees with the Applicant statement that the urinary symptoms were transient and not clinically meaningful, as limitations in the PRO assessment methods noted above limit the ability to accurately draw conclusions. Overall, the FDA considers the PRO assessments in ENVISION and ATLAS to show some worsening of urinary symptoms during UGN-102 treatment, which may or may not be clinically meaningful, and the peak severity and timing of resolution of these symptoms is unclear.

**FDA's Figure 16 Change from Baseline in EORTC QLQ-NMIBC24 Urinary Symptom Scale**




These PRO analyses use the same analysis set used for the efficacy analyses. 17 ENVISION patients and 10 ATLAS patients were excluded from analyses after clinical eligibility review.

Although the experience collected from patients is important to collect, the FDA views qualitative patient interview data from ENVISION exploratory information collected from a small set of patients and cannot be used in this context as supportive evidence. In general, qualitative interview information can be helpful for understanding the disease context, and is less reliable for evaluating the benefits and risks of a treatment, particularly in the setting where objective measures are rigorously being collected and in single arm trials.

# 5 Other Significant Issues Pertinent to Clinical Conclusions on Efficacy and Safety

## 5.1 Applicability of the UGN-102 Study Results to the United States Population

The Applicant's Position:

Results from the late-phase clinical studies are applicable to the general US population with LG-IR-NMIBC. This conclusion is based on the similarities between the demographics of patients in the UGN-102 late-phase clinical trials and those reported in the literature of real-world US patients with LG-IR-NMIBC, and the consistent efficacy demonstrated across subgroups, including region.

The UGN-102 clinical studies were rigorously conducted and evaluation of response was based on internationally accepted standard urological practice (white light cystoscopy, histopathology, urine cytology) and the definition of CR and DOR was the same in all studies

(Section 2.2). Sites were trained on definitions of CR and NCR/recurrence as defined in the study protocols. Finally, efficacy analyses were based on central pathology review (discussed in the context of the pivotal ENVISION trial in Section 2.2.1).

In the United States, NMIBC typically affects older adults and more frequently men, with a median age at diagnosis of 73 years.[2,3] The age and sex distribution of the study populations in ENVISION, OPTIMA II, and ATLAS are reflective of the general US NMIBC population. Across the 3 studies, the median age was 70 years, and most patients were male (63% of patients).

Most patients with NMIBC in the United States are White (89.52%) (Section 2.1.1), and the study populations in ENVISION, OPTIMA II, and ATLAS were >96% White. In the pivotal trial, ENVISION, despite having 100% of US sites in urban settings, with a mix of academic and community practices (Section 2.2.1.1), there was a lack of racial diversity during enrollment. This follows a trend among other NMIBC studies, where clinical trials across all phases typically enroll a majority White patient population.[9,53]

Finally, the subgroup analyses were generally consistent across all subgroups evaluated in the pivotal trial, ENVISION (Section 2.3.1.5). Subgroup analyses of DOR were consistent across baseline demographics except for region, where it was lower in US patients than in non-US patients. This was likely due to the fact that most US patients had multiple prior recurrences, a population that tends to have shorter DOR. In the subgroup analyses for 3-month CRR, however, there was no such difference (Figure 8).

The totality of evidence supports the applicability of the results of the UGN-102 clinical trials to the general US population with LG-IR-NMIBC.

The FDA's Position: In the ATLAS trial patients did not receive a single post-TURBT intravesical installation of chemotherapy, which is recommended by professional guidelines in the U.S. for most patients with intermediate- risk NMIBC, and the control arm thus does not represent the most active standard of care. Otherwise, the FDA does not have any concerns regarding the applicability of the submitted data to a U.S. patient population.

# 6 Points for the Advisory Committee to Consider

The Applicant's Position:

## 6.1 Benefits of UGN-102

LG-IR-NMIBC is a highly recurrent disease that is inadequately controlled with current US community-based care—TURBT ± IVT. The risk of recurrence in this population is high 1 year after TURBT ± IVT, and most patients will have multiple recurrences requiring repetitive TURBTs under general anesthesia during their disease course.[7,20] There are currently no FDA-approved drug therapies for recurrent LG-IR-NMIBC, and there is a high unmet need for new treatment options that can increase recurrence-free survival and decrease the overall burden of repeated TURBTs under general anesthesia. UGN-102 produces CRs in patients with recurrent LG-IR-

NMIBC that are more durable than with TURBT, as demonstrated in the ATLAS trial. Additionally, UGN-102 is administered in an office-based setting, without general anesthesia, and intravesical instillation of chemotherapy is a simple, well-known procedure for urology practices. Patients generally can resume their activities of daily living shortly after UGN-102 instillation. Further, UGN-102 has the potential to reduce the need for repetitive TURBTs in an older patient population with significant comorbidities and polypharmacy, including anticoagulation, and the associated risks of general anesthesia.

The totality of the data from the late-phase studies demonstrates that UGN-102 provides robust, clinically meaningful, and durable control of recurrent LG-IR-NMIBC that is better than with TURBT. In ENVISION, treatment with UGN-102 achieved a clinically meaningful 77.6% CRR that was maintained after 18 months of follow-up in >80% of patients. In ATLAS, the direct comparison of UGN-102 alone versus TURBT demonstrated an improved 3-month CRR and a meaningful improvement in DOR with UGN-102. Furthermore, UGN-102 did not negatively impact health-related QoL, and 90% of patients who had experienced both interventions strongly preferred UGN-102 over TURBT. Interviewed patients reported that treatment with UGN-102 resulted in less impact on activities/responsibilities (e.g., work, recreation and exercise, and sexual activity) than TURBT. Patients would recommend UGN-102 as it was perceived to be less invasive, less painful, and less time-consuming than TURBT.

Data from the pivotal ENVISION study and supportive studies are consistent and demonstrate that UGN-102 is an efficacious outpatient treatment for recurrent LG-IR-NMIBC that provides a longer recurrence-free interval than TURBT and can reduce the need for TURBT under general anesthesia.

## 6.2 Risks of UGN-102

Overall, the safety profile of UGN-102 is acceptable and manageable. As expected, TEAEs were mainly localized to the lower urinary tract, consistent with intravesical chemotherapy. These localized lower urinary tract symptoms mostly occurred in the first 3 months and were of limited duration. TEAEs were mostly low grade in severity and manageable as part of standard urological practice. Few patients discontinued treatment due to AEs, and few patients reported treatment- or procedure-related SAEs. The frequency of Grade ≥3 and serious TEAEs within the Renal and Urinary Disorders SOC (where TEAEs were most commonly reported) was low.

Treatment with UGN-102 results in minimal systemic absorption of mitomycin and is associated with a low risk of systemic side effects. No clinically meaningful risk of bone marrow suppression was observed across studies. The safe administration of UGN-102 can be adequately described in the label, and routine pharmacovigilance to monitor risks can be conducted in a post-marketing setting.

## 6.3 Benefit–Risk Conclusions

Overall, UGN-102 has a positive benefit–risk profile for the treatment of adults with recurrent LG-IR-NMIBC. The totality of data supports UGN-102 as a safe and efficacious treatment option for recurrent LG-IR-NMIBC that produces higher CRs and more durable responses than TURBT.

In contrast to TURBT, UGN-102 has the potential to treat tumors too small to visualize via its field effect. The reverse thermal properties of the hydrogel enable prolonged exposure of tumor sites and adjacent areas to high concentrations of mitomycin, unlike aqueous IVT. Importantly, the hydrogel and method of administration optimizes drug delivery while minimizing systemic drug exposure and systemic effects.

UGN-102 offers patients a treatment option that does not require general anesthesia and that does not worsen QoL or severely impact activities of daily living, which can be resumed shortly after UGN-102 instillation.

UGN-102 can be used in selected patients to delay disease recurrence and reduce the burden of repeated TURBTs under general anesthesia in an older patient population with significant comorbidities and polypharmacy, including anticoagulation, filling an unmet need for this patient population. UGN-102 is an alternative in-office treatment option that has the potential to reduce the number of TURBTs by providing a durable recurrence-free interval.

The FDA's Position: The FDA considers CR to reflect drug activity as LG-IR-NMIBC lesions would not be expected to resolve spontaneously in the absence of treatment and agrees the Applicant has demonstrated activity for UGN-102 in patients with recurrent LG-IR-NMIBC based on the CRR of 77.6% (95% CI: 71.5, 82.9) observed in ENVISION, which was consistent in ATLAS. The FDA does not agree with the statement that the CR rate for UGN-102 was higher or more durable than that for TURBT as ATLAS was not adequately designed to address this question.

The clinical meaningfulness of a CR depends both on its durability as well as the morbidity of any subsequent treatment that may be avoided or delayed due to the CR. For patients with LG-IR-NMIBC, the alternative and likely subsequent therapy, TURBT (with or without peri-operative or adjuvant treatment), has relatively lower morbidity than radical cystectomy or radical nephroureterectomy, which were the alternative procedures intended to be avoided in other single-arm trials used for drug approval in non-muscle-invasive urothelial carcinoma. Additionally, because ENVISION was a single-arm trial with no comparator arm, interpreting the durability of CR with UGN-102 is challenging, as it is unclear whether the DOR observed was due to the study intervention rather than reflecting the natural history of LG-IR-NMIBC.

Further, the Applicant's proposed utility of UGN-102 as a therapy that may "reduce the burden of repeated TURBTs under general anesthesia in the elderly, comorbid, LG-IR-NMIBC population" is unclear because of lack of long-term data collected on future treatments.

Toxicity associated with UGN-102 was primarily related to the genitourinary tract and was low-grade. However, patients remained at risk for a for toxicity during the entire 6-week treatment

period and for several weeks afterwards, which is longer than the duration of toxicity expected for TURBT and the Applicant has not demonstrated that treatment with UGN-102 is safer or more tolerable than TURBT. These toxicities may be considered acceptable by some patients if UGN-102 allows for a durable CR that delays or obviates the need for further treatment. However, there are uncertainties regarding the assessment of DOR as noted above. If patients do not recur as frequently as the Applicant claims, exposing them to toxicity of UGN-102 may not result in a favorable benefit-risk assessment.

A randomized clinical trial evaluating a time-to-event endpoint such as disease-free survival, using the same endpoint definition on both arms, may have mitigated the concerns identified in the FDA's review. This trial design would have allowed for establishing efficacy and characterizing the natural history of the disease in the context of a control, obtaining data on the need for and outcomes after subsequent therapy (e.g., TURBT), mitigating concerns with respect to potential variability associated with disease assessments (e.g., inter-operator TURBT assessment, inter-observer pathology assessments), obtaining quality patient-reported outcome data, and robustly characterizing safety.

# 7 Draft Topics for Discussion by the Advisory Committee

FDA asks the committee to discuss whether durable complete response assessed in a single-arm trial can establish efficacy in this low-grade, intermediate-risk, non-muscle invasive bladder cancer (LG-IR-NMIBC) population.

The voting question is as follows:

Is the overall benefit-risk of the investigational therapy UGN-102 favorable in patients with recurrent LG-IR-NMIBC?

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# 9 Appendices

## Appendix 1: Summary of the UGN-102 Clinical Development Program

Eight clinical studies make up the UGN-102 clinical development program. These studies were performed according to consensus ethical principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable laws and regulations.

- 1 Phase 1 single-dose study in patients with muscle invasive bladder cancer (MIBC) scheduled to undergo radical cystectomy (BL001)
- 3 Phase 2 dose-ranging studies in patients with LG or HG NMIBC (BL002, BL003, and BL004)
- 4 late-phase studies of the target UGN-102 dose/regimen (75 mg mitomycin instilled once weekly for 6 weeks into the bladder via a urinary catheter) in patients with LG-IR-NMIBC:
  - ENVISION (BL011): Pivotal Phase 3, open-label, single-arm study in recurrent LG-IR-NMIBC
  - ATLAS (BL006): Phase 3, open-label, randomized, controlled study in patients with newly diagnosed and recurrent LG-IR-NMIBC comparing UGN-102 with TURBT alone
  - OPTIMA II (BL005): Phase 2b, open-label, single-arm study in patients with newly diagnosed and recurrent LG-IR-NMIBC
  - Home instillation study (BL010): Phase 3b, open-label, single-arm study in patients with newly diagnosed and recurrent LG-IR-NMIBC evaluating the feasibility of home instillation of UGN-102

Across these studies, 536 patients were exposed to UGN-102 at any dose. In the early phase studies (BL001, BL002, BL003, and BL004), 87 patients received single or multiple intravesical doses of UGN-102. In the 4 Phase 2/3 studies (ENVISION, OPTIMA II, ATLAS, and a small home instillation study), 449 patients received UGN-102 at the target dose/regimen of UGN-102 for treatment of patients with LG-IR-NMIBC.

## Appendix 2: Summary of Regulatory Interactions with the US FDA

Table 9 provides a summary of the key interactions between the Sponsor and the FDA during the development of UGN-102.

**Table 9 Regulatory Interactions**

| Description | Date | Meeting Outcome |
|---|---|---|
| Pre-IND Type B | June 2016 | UroGen proposed supporting approval of UGN-102 with a single-arm study evaluating CRR at 3 months (primary) and 12 months (secondary). The Agency did not agree and recommended a randomized controlled study. |
| End-of-Phase 2 Type B | November 2017 | UroGen proposed a single-arm approach that included evaluation of patients unable to undergo TURBT. The Agency did not agree and recommended a randomized controlled study. |
| Guidance 3 Type C | January 2020 | UroGen proposed a randomized controlled study comparing UGN-102 and TURBT using a non-inferiority approach with a time to event endpoint. The Agency did not agree and recommended a study |

| | | |
|---|---|---|
| | | with a superiority design with an appropriate primary endpoint addressing multiple FDA concerns over the proposed study. |
| Guidance Type B | May 2020 | UroGen proposed a randomized controlled study (ATLAS) comparing UGN-102 and TURBT using a superiority design, with a noninferiority test, with disease-free survival as the primary endpoint. In the preliminary comments, the Agency noted the superiority design in general was acceptable but did not agree with the noninferiority test. They continued to express concerns including the different definitions of DFS used in each arm and the confounding of results due to the hybrid nature of the primary intervention. |
| Pre-NDA Type B | December 2020 | UroGen proposed to submit an NDA under the accelerated approval pathway based on an intermediate clinical endpoint (robust CRR in the Phase 2 study OPTIMA II) and proposed that the clinical benefit would be verified in the ongoing Phase 3 study (ATLAS). The Agency did not agree with this approach and advised on continued discussions on the study design for ATLAS. |
| Guidance Type B | May 2021 | This meeting was to discuss the Agency's concerns over the design of the ongoing study ATLAS, and UroGen incorporated most of the Agency's advice when drafting a subsequent amendment to the protocol, but full agreement was not reached on the measurement of DFS and the hybrid nature of the UGN-102 ± TURBT intervention. |
| Guidance Type C | August 2021 | UroGen discussed alternative development pathways including a restricted indication, a placebo-controlled study, and a single-arm approach. The Agency advised that a single-arm approach may possibly serve as a major study to support an approval if it enrolls a large number of patients, includes sufficient duration of follow up, and demonstrates sufficient efficacy and safety that encompasses outcomes with later TURBT procedures. |
| Guidance Type C | November 2021 | UroGen proposed the single-arm study (ENVISION) meeting the criteria set out by the FDA in the August 2021 meeting. Following additional feedback, a modified protocol was submitted to the IND for final review. |
| Pre-NDA CMC Type B | July 2023 | The content, format, and cross-referencing strategy for the CMC sections of the NDA were agreed, as was the cross-referencing strategy for the nonclinical sections. The Agency agreed to a rolling review. |
| Pre-NDA Type B | September 2023 | UroGen provided top line results of the ENVISION study and proposed a content plan for an NDA. The content, format, and pooling strategy were agreed at the meeting. FDA required that the NDA contained the results from all patients at 12 months follow up. |
| Mid Cycle meeting | March 2025 | FDA provided the Sponsor with existing review issues and discussed alignment on the analysis population to be presented at ODAC. As part of this alignment, UroGen and FDA agreed to change the indication statement to focus on recurrent disease—the population used in the pivotal trial ENVISION. |

CMC=chemistry, manufacturing, and controls; CRR=complete response rate; DFS=disease-free survival; FDA=Food and Drug Administration; IND=Investigational New Drug; NDA=New Drug Application; ODAC=Oncologic Drugs Advisory Committee; Ref=reference; TURBT=transurethral resection of bladder tumor.

## Appendix 3: Precedent for the Pivotal Trial Study Design

Evidence in the literature suggests that tumor status at 3 months is a significant prognostic factor for recurrence. The European Association of Urology guidelines on NMIBC acknowledge

follow-up at the 3-month time point post-TURBT as an important indicator for recurrence and progression.[18] In a study of 115 patients with G1Ta disease followed for a mean of 19.4 years, significantly more patients who had recurrence at 3 months had further recurrence at 1 year compared with those who were tumor-free at 3 months (55.8% vs 17.8%, p = 0.0007).[19] The recurrence rates of those with tumor at 3 months remained persistently higher at 5 years, with a 1 in 2 chance of recurrence.[19] This compares poorly to those who were tumor-free at 3 months in whom the risk was 1 in 8.[19] Complete response at 3 months is a relevant and clinically meaningful endpoint to evaluate effectiveness of treatment in NMIBC.

Discussions between the Sponsor and the Agency regarding the appropriateness of ENVISION to serve as the pivotal trial for UGN-102 align with recent new drug approvals in BCG-unresponsive NMIBC. Prior FDA guidance on clinical trial endpoints for the approval of cancer drugs stated that "[t]reatment effect measured by CR. . . can represent direct clinical benefit based on the specific disease, context of use, magnitude of the effect, effect duration, disease setting, location of disease, available therapy, and the risk-benefit relationship."[54] The endpoints used in ENVISION demonstrate magnitude of effect (CRR) and effect duration (DOR).

The primary and key secondary endpoint of ENVISION were determined in consultation with the Agency, are appropriate for a single-arm study based on FDA guidance, and align with prior approvals in this disease setting. ENVISION enrolled a large number of patients (n=240), and sample size was based on CRR and DOR considerations. ENVISION included adequate follow-up, with data up to at least 18 months after 3-month CR included in the NDA and with follow-up of ongoing patients continuing up to 5 years. Finally, ENVISION demonstrated efficacy, and the safety profile was as expected, with mild to moderate urinary symptoms that can be managed in everyday urologic practice. Importantly, there was no increase in the rate of complications in TURBTs performed after treatment with UGN-102.

Furthermore, precedent for full approval based on single-arm pivotal trials is established based on recent approvals in NMIBC, summarized in Table 10. Like the design of ENVISION, these trials all used CRR as the primary efficacy endpoint and DOR as the secondary endpoint.

**Table 10 Full Approvals in NMIBC Based on Single-Arm Trials**

| Drug | Indication | Approval | Pivotal Trial | Endpoints per USPI: Primary<br>Secondary |
|---|---|---|---|---|
| Keytruda[55] | BCG-unresponsive, high-risk NMIBC with CIS with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy | Jan 2020 | Single-arm, Phase 2 KEYNOTE-057 (NCT02625961) (N=96) | **CRR at 3 months**<br>DOR |
| Adstiladrin[56] | High-risk BCG-unresponsive NMIBC with CIS with or without papillary tumors | Dec 2022 | Single-arm, Phase 3 CS-003 (NCT02773849) (N=98) | **CR within 12 months**<br>DOR |

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|---|---|---|---|---|
| Anktiva[57] | In combination with BCG for BCG-unresponsive NMIBC with CIS with or without papillary tumors | Apr 2024 | Single-arm, Phase 2/3 QUILT-3.032 (NCT03022825) (N=77) | **CR within 6 months**<br>DOR |

BCG=Bacillus Calmette-Guérin; CIS=carcinoma in situ; CR=complete response; CRR=complete response rate; DOR=duration of response; NMIBC=non-muscle invasive bladder cancer; USPI=United States Prescribing Information.

## Appendix 4: Key Inclusion and Exclusion Criteria

**Table 11 Key Inclusion and Exclusion Criteria**

| Key Inclusion Criteria | Key Exclusion Criteria |
|---|---|
| • LG-NMIBC (Ta) histologically confirmed by cold cup biopsy at screening or within 8 weeks before screening<br>• History of LG-NMIBC requiring treatment with TURBT (ENVISION only)<br>• Intermediate risk disease, defined as having 1 or 2 of the following<br>– Presence of multiple tumors<br>– Solitary tumor >3 cm<br>– Early or frequent recurrence (≥1 occurrence of LG-NMIBC within 1 year of the current diagnosis)<br>• Negative voiding cytology for HG disease within 8 weeks (ENVISION) or 6 weeks (ATLAS) before screening | • Received BCG treatment for UC in the past 1 year<br>• History of HG papillary bladder cancer in the past 2 years<br>• History of CIS in the past 2 years (ENVISION) or 5 years (ATLAS)<br>• Clinically significant urethral stricture that would preclude passage of a urethral catheter<br>• Any condition that would prohibit normal voiding<br>• Past or current muscle invasive bladder cancer (i.e., T2, T3, T4) or metastatic UC<br>• Current tumor stage of T1<br>• Concurrent UTUC<br>• IVCT in the past 2 years (ENVISION) or any history (ATLAS) except for a single dose post-TURBT |

BCG=Bacillus Calmette-Guérin; CIS=carcinoma in situ; HG=high-grade; IVCT=intravesical chemotherapy; LG=low-grade; NMIBC=non-muscle invasive bladder cancer; TURBT=transurethral resection of bladder tumor; UC=urothelial carcinoma; UTUC=upper tract urothelial carcinoma.

## Appendix 5: Statistical Analysis Methods (Pivotal Phase 3 Trial ENVISION)

### Analysis Populations for Primary and Secondary Endpoints:

- **ITT:** All patients who were enrolled into the study and treated with UGN-102 (also referred to as the safety analysis set). The analysis of the primary endpoint CRR at the 3-month Visit, analyses of patient-reported measures, and safety analyses were performed using this analysis set.
- **3-month CR:** The subset of patients in the ITT Analysis Population who achieved a CR at the 3-month disease assessment. This analysis set excluded all patients who had either a missing or indeterminate response at the 3-month disease assessment. The key secondary endpoint (DOR) and other secondary endpoints (DFS and DCR rates at scheduled disease assessment time points) were performed in this analysis set.
- **FDA Analysis Population:** All treated patients who met the strict per-protocol definition of LG-IR-NMIBC, had recurrent disease (defined as a history of LG-NMIBC treated with TURBT), and had no major protocol deviation that would confound the efficacy evaluation.

### Primary Endpoint:

CRR was analyzed based on the data observed in the ITT Analysis Population. The exact 2-sided 95% CI for CRR was derived using the Clopper-Pearson method. Reasons for NCR comprised

residual disease, progression, and indeterminate and were tabulated using the numbers and percentages of patients.

The date of disease assessment associated with either CR or NCR was determined using the earliest date of cystoscopy, biopsy, or cytology. If a response could not be evaluated for a patient at the 3-month Visit, the patient was considered as NCR for the purpose of the analysis and was included in the denominator of the CRR.

Prespecified subgroup analyses for CRR were performed in the ITT Analysis Population based on various demographic factors and disease-related characteristics (e.g., tumor burden, tumor count, previous NMIBC episodes, prior TURBT).

### Key Secondary Endpoint:

The DOR analysis, performed in the 3-month CR analysis set, was calculated in months as

(first event date / censored date – date of first documented CR + 1) / 30.4375.

The distribution of DOR was estimated using the KM method. Median times of DOR, first and third quartiles, and 95% CI were estimated. The median follow-up time along with 95% CI was estimated using the inverse KM method. Prespecified subgroup analyses for DOR were performed as described for the primary endpoint (CRR).

### Other Secondary Endpoints:

DCR rates at scheduled disease assessment time points were summarized in the 3-month CR analysis set using a denominator of all patients who had a CR at the 3-month Visit. Patients who had an indeterminate response or missed a visit had the response imputed according to prespecified rules prior to conducting the analyses.

### Safety Analysis:

Safety analyses were based on the safety analysis set and included summaries of TEAEs by observation period (overall, up to 3 months, and post 3 months), deaths, serious TEAEs, TEAEs leading to treatment or study discontinuation, AESIs (allergic reactions, bone marrow suppression, genitourinary infections, LUTS, voiding interruption due to urethral/penile edema unrelated to prostatic hypertrophy), clinical laboratory assessments, vital signs, physical examinations, and urology-oriented examinations.

## Appendix 6: Summary of Efficacy – ITT Analysis Population (ENVISION, OPTIMA II, and ATLAS)

### Pivotal Phase 3 Study ENVISION Results – ITT Analysis Population

**Table 12 Summary of Demographics and Baseline Characteristics – ITT Analysis Population (ENVISION)**

| Characteristic<br>Statistic | UGN-102<br>(N=240) |
|---|---|
| Age (years) | |
| n | 240 |

| Characteristic<br>Statistic | UGN-102<br>(N=240) |
|---|---|
| Mean (SD) | 68.8 (11.59) |
| Median (min, max) | 70.0 (30, 92) |
| Age group (years), n (%) | 240 |
| <65 | 78 (32.5) |
| ≥65 to <75 | 73 (30.4) |
| ≥75 to <85 | 76 (31.7) |
| ≥85 | 13 (5.4) |
| Sex, n (%) | 240 |
| Male | 147 (61.3) |
| Female | 93 (38.8) |
| Race, n (%) | 240 |
| American Indian or Alaska Native | 0 |
| Asian | 2 (0.8) |
| Black or African American | 3 (1.3) |
| Native Hawaiian or Other Pacific Islander | 0 |
| White | 234 (97.5) |
| Not reported | 1 (0.4) |
| Ethnicity, n (%) | 240 |
| Hispanic or Latino | 3 (1.3) |
| Not Hispanic or Latino | 237 (98.8) |

Age is calculated from date of birth to date of consent. Percentages are computed using the number of patients with non-missing data as the denominator. For missing data, percentages are computed using N as the denominator. ITT=intent-to-treat; SD=standard deviation.
Source: BL011-CSR-Table 14.1.6.1

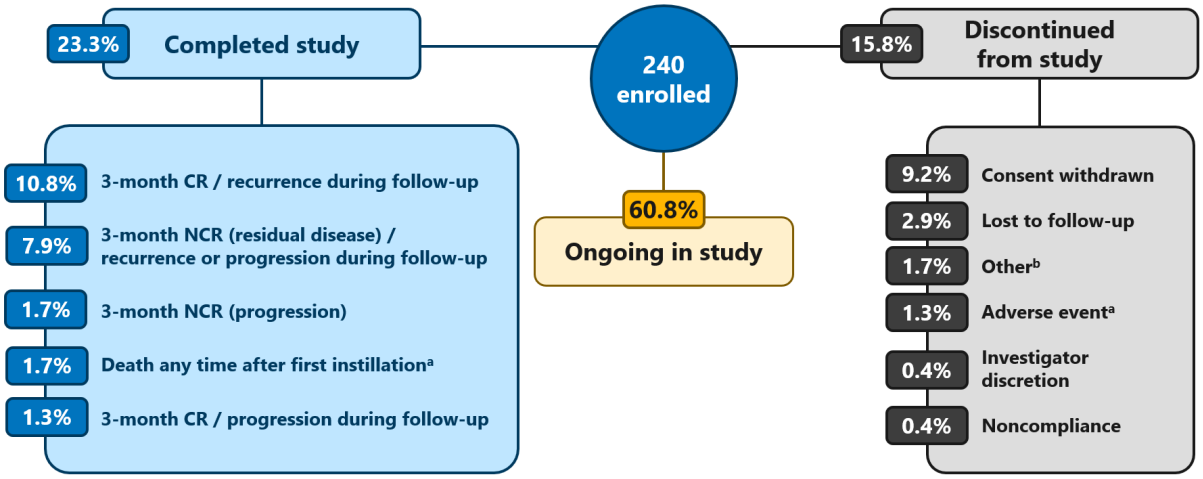
## Table 13 Summary of Baseline Disease Characteristics – ITT Analysis Population (ENVISION)

| Characteristic<br>Statistic | UGN-102<br>(N=240)<br>n (%) |
|---|---|
| Treatment course (instillations) | 240 |
| 6 | 228 (95.0) |
| <6 | 12 (5.0) |
| Longest tumor diameter (cm)[a] | 235 |
| ≤3 | 216 (91.9) |
| >3 | 19 (8.1) |
| Missing | 5 (2.1) |
| Tumor burden (cm)[b] | 221 |
| ≤3 | 180 (81.4) |
| >3 | 41 (18.6) |
| Missing | 19 (7.9) |
| Tumor count | 239 |
| Single | 41 (17.2) |
| Multiple | 198 (82.8) |
| Missing | 1 (0.4) |
| Previous NMIBC episodes | 240 |
| Yes | 232 (96.7) |
| No[c] | 8 (3.3) |

| Characteristic<br>Statistic | UGN-102<br>(N=240)<br>n (%) |
|---|---|
| Previous NMIBC episodes within 1 year of the current diagnosis | 240 |
| Yes | 124 (51.7) |
| No | 116 (48.3) |
| Number of previous NMIBC episodes | 240 |
| 0[c] | 8 (3.3) |
| 1 | 144 (60.0) |
| 2 | 35 (14.6) |
| >2 | 53 (22.1) |
| Previous LG-NMIBC episodes | 240 |
| Yes | 229 (95.4) |
| No[c] | 11 (4.6) |
| Previous LG-NMIBC episodes within 1 year of the current diagnosis | 240 |
| Yes | 124 (51.7) |
| No | 116 (48.3) |
| Number of previous LG-NMIBC episodes | 240 |
| 0[c] | 11 (4.6) |
| 1 | 145 (60.4) |
| 2 | 37 (15.4) |
| >2 | 47 (19.6) |
| Number of prior TURBT to treat NMIBC | 240 |
| 0[c] | 8 (3.3) |
| 1 | 152 (63.3) |
| 2 | 33 (13.8) |
| >2 | 47 (19.6) |
| Number of prior TURBT to treat LG-NMIBC | 240 |
| 0[c] | 12 (5.0) |
| 1 | 152 (63.3) |
| 2 | 35 (14.6) |
| >2 | 41 (17.1) |
| Smoking history[d] | 240 |
| Non-smoker | 112 (46.7) |
| Smoker | 128 (53.3) |

[a]Longest tumor diameter is defined as the longest diameter among all measurable lesions. [b]Tumor burden (cm) is defined as the sum of the longest diameters of measurable lesions. [c]History of LG-NMIBC requiring treatment with TURBT was an inclusion criterion for the study. A protocol deviation was recorded for patients who enrolled in the study who did not meet that criterion. [d]Smoker category includes both former and current smokers. Non-smoker category includes "Never." Percentages are computed using the number of patients with non-missing data as the denominator. For missing data, percentages are computed using N as the denominator. ITT=intent-to-treat; LG=low-grade; NMIBC=non-muscle invasive bladder cancer; TURBT=transurethral resection of bladder tumor.
Source: BL011-CSR-Table 14.1.6.2

**Figure 17 Patient Disposition – ITT Analysis Population (ENVISION)**




Data cutoff October 2, 2024.
[a]Number of patients who discontinued from study due to AE does not include patients with fatal TEAEs who are categorized as completed study due to death any time after first instillation. [b]Two patients were discontinued due to having no residual tumor prior to UGN-102 instillation, 1 patient did not want to receive any of the offered SoC treatment modalities, and 1 patient informed the site that he had elected to go to another hospital. AE=adverse event; CR=complete response; ITT=intent-to-treat; NCR=non-complete response; SoC=standard of care; TEAE=treatment-emergent adverse event.
Source Dataset: BL011-M21-ITT Analysis Set-ADSL

**Table 14 Summary of Efficacy – ITT Analysis Population (ENVISION)**

| Endpoint | Patients (N=240) | 95% Confidence Interval |
|---|---|---|
| **CR rate (ITT analysis set), n/N (%)** | 184/240 (76.7) | 70.8, 81.9 |
| **DOR (3-month CR analysis set), KM estimate, %** | | |
| 12 months after 3-month CR | 83.6 | 77.2, 88.3 |
| 18 months after 3-month CR | 81.6 | 75.0, 86.6 |
| **DCR rates (3-month CR analysis set), n/N (%)** | | |
| 3 months after 3-month CR | 167/184 (90.8) | 85.6, 94.5 |
| 6 months after 3-month CR | 160/184 (87.0) | 81.2, 91.5 |
| 9 months after 3-month CR | 147/184 (79.9) | 73.4, 85.4 |
| 12 months after 3-month CR | 143/184 (77.7) | 71.0, 83.5 |
| 15 months after 3-month CR | 139/184 (75.5) | 68.7, 81.6 |
| 18 months after 3-month CR | 129/184 (70.1) | 62.9, 76.6 |

CR=complete response; DCR=durable complete response; DOR=duration of response; ITT=intent-to-treat.
Source: BL011-CSR-Table 14.2.1.1; BL011-M21-Durability Update-Table 14.2.2.2; Table 14.2.3.1.1.1

## Supportive Phase 2b Study OPTIMA II Results – ITT Analysis Population

### *Demographics and Baseline Disease Characteristics – ITT Analysis Population*

A total of 63 patients were enrolled and treated with UGN-102 in OPTIMA II, and 57 (90.5%) completed 6 instillations. The median age of patients was 68.0 (range, 33-96) years. Most patients were male (60.3%) and White (87.3%). Of the 63 patients enrolled, 49 (77.8%) had recurrent LG-NMIBC at study entry, and 28 (44.4%) had a previous episode within 1 year of the current diagnosis. Patients with recurrent disease had a mean of 4.0 (range, 0-13) prior TURBT procedures, with 37 patients (75.5%) having ≥2 prior TURBT procedures, and 28 patients

(57.1%) having ≥3 prior TURBT procedures. Of 61 patients with available baseline data, 50 (82.0%) had multiple visible tumors and 17 (27.9%) had a total tumor burden >3 cm.

**Table 15 Summary of Efficacy – ITT Analysis Population (OPTIMA II)**

| Endpoint | Patients (N=63) | 95% Confidence Interval |
|---|---|---|
| **CR rate (ITT analysis set), n/N (%)** | 41/63 (65.1) | 52.0, 76.7 |
| **DOR (3-month CR analysis set), KM estimate, %** | | |
| 9 months after 3-month CR | 69.9 | 51.8, 82.3 |
| **DCR rates (3-month CR analysis set), n/N (%)** | | |
| 3 months after 3-month CR | 39/41 (95.1) | 83.5, 99.4 |
| 6 months after 3-month CR | 29/41 (70.7) | 54.5, 83.9 |
| 9 months after 3-month CR | 23/41 (56.1) | 39.7, 71.5 |

CR=complete response; DCR=durable complete response; DOR=duration of response; ITT=intent-to-treat.
Source: ISE-Table 14.2.1.1.1; Table 14.2.2.1.2.1; Table 14.2.2.2.1.1

### Supportive Phase 3 Study ATLAS Results – ITT Analysis Population

**Table 16 Summary of Demographics and Baseline Characteristics – ITT Analysis Population (ATLAS)**

| Characteristic Statistic | UGN-102 (N=142) | TURBT (N=140) |
|---|---|---|
| Age (years) | | |
| n | 142 | 140 |
| Mean (SD) | 66.7 (10.59) | 66.3 (10.50) |
| Median (min, max) | 68.0 (23, 85) | 67.0 (29, 88) |
| Age group (years), n (%) | | |
| <65 | 51 (35.9) | 63 (45.0) |
| ≥65 to <75 | 59 (41.5) | 47 (33.6) |
| ≥75 to <85 | 29 (20.4) | 27 (19.3) |
| ≥85 | 3 (2.1) | 3 (2.1) |
| Sex, n (%) | | |
| Male | 105 (73.9) | 93 (66.4) |
| Female | 37 (26.1) | 47 (33.6) |
| Race, n (%) | | |
| American Indian or Alaska native | 0 | 0 |
| Asian | 1 (0.7) | 1 (0.7) |
| Black or African American | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 |
| White | 140 (98.6) | 139 (99.3) |
| Not reported | 1 (0.7) | 0 |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 2 (1.4) | 1 (0.7) |
| Not Hispanic or Latino | 140 (98.6) | 137 (97.9) |
| Not reported | 0 | 2 (1.4) |

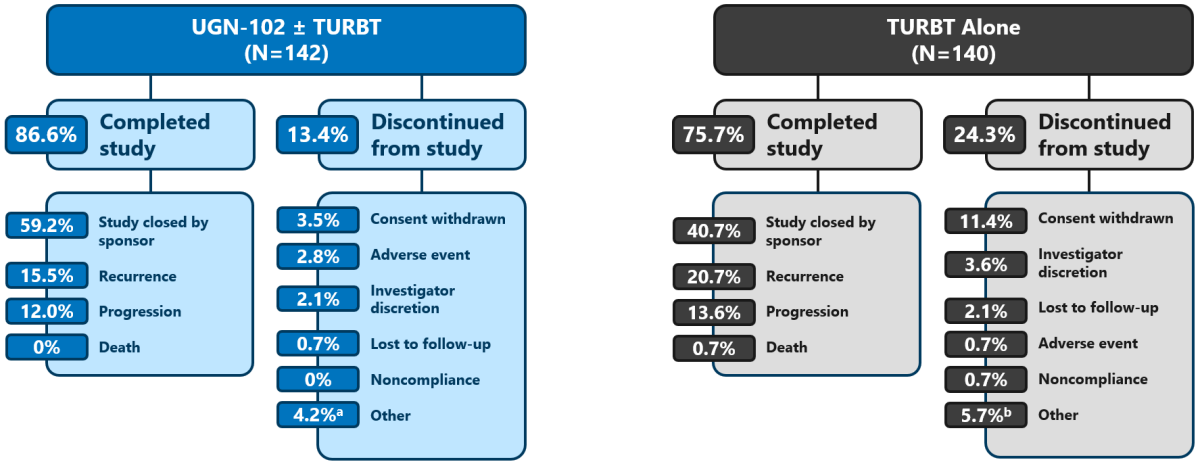
Age was calculated from date of consent and date of birth. Percentages were computed using the number of patients in ITT Analysis Population with a response value for a corresponding characteristic as the denominator.
ITT=intent-to-treat; SD=standard deviation; TURBT=transurethral resection of bladder tumor.
Source: ISE-Table 14.1.2.1

**Table 17 Summary of Baseline Disease Characteristics – ITT Analysis Population (ATLAS)**

| Characteristic<br>Statistic | UGN-102<br>(N=142)<br>n (%) | TURBT<br>(N=140)<br>n (%) |
|---|---|---|
| Treatment course (instillations) | 142 | NA |
| 6 | 132 (93.0) | NA |
| <6 | 10 (7.0) | NA |
| Longest tumor diameter (cm)[a] | 138 | 138 |
| ≤3 | 97 (70.3) | 110 (79.7) |
| >3 | 41 (29.7) | 28 (20.3) |
| Missing | 4 (2.8) | 2 (1.4) |
| Tumor burden (cm)[b] | 136 | 132 |
| ≤3 | 69 (50.7) | 73 (55.3) |
| >3 | 67 (49.3) | 59 (44.7) |
| Missing | 6 (4.2) | 8 (5.7) |
| Tumor count | 136 | 134 |
| Single | 54 (39.7) | 40 (29.9) |
| Multiple | 82 (60.3) | 94 (70.1) |
| Missing | 6 (4.2) | 6 (4.3) |
| Previous NMIBC episodes[c] | 142 | 140 |
| Yes | 57 (40.1) | 66 (47.1) |
| No | 85 (59.9) | 74 (52.9) |
| Previous NMIBC episodes within 1 year of the current diagnosis[c] | 142 | 140 |
| Yes | 35 (24.6) | 39 (27.9) |
| No | 107 (75.4) | 101 (72.1) |
| Number of previous NMIBC episodes[c] | 142 | 140 |
| 0 | 85 (59.9) | 74 (52.9) |
| 1 | 32 (22.5) | 33 (23.6) |
| 2 | 11 (7.7) | 14 (10.0) |
| >2 | 14 (9.9) | 19 (13.6) |
| Number of prior TURBT to treat NMIBC[c] | 142 | 140 |
| 0 | 87 (61.3) | 75 (53.6) |
| 1 | 30 (21.1) | 35 (25.0) |
| 2 | 13 (9.2) | 13 (9.3) |
| >2 | 12 (8.5) | 17 (12.1) |
| Smoking history[d] | 142 | 140 |
| Non-smoker | 63 (44.4) | 73 (52.1) |
| Smoker | 79 (55.6) | 67 (47.9) |

[a]Longest tumor diameter is the longest diameter among all measurable lesions. [b]Tumor burden is calculated as the sum of the longest diameters of the measurable lesions. [c]Based on data from the Urothelial Carcinoma Medical History eCRF. [d]The smoker category includes both former and current smokers, and the non-smoker category includes "Never." Percentages are computed using the number of non-missing data as the denominator. For missing data, percentages are computed using N as the denominator. eCRF=electronic case report form; ITT=intent-to-treat; NMIBC=non-muscle invasive bladder cancer; TURBT=transurethral resection of bladder tumor.
Source: ISE-Table 14.1.2.2

**Figure 18 Patient Disposition – ITT Analysis Population (ATLAS)**




[a]"Other" reasons for discontinuation were "randomization error" for 3 patients and "sponsor requirement," "not eligible," and "independently applied to another medical center" for 1 patient each. [b]"Other" reasons for discontinuation were "not eligible" for 3 patients, "disease progression" for 2 patients, and "sponsor requirement," "patient decision," and "new lesions identified, however biopsy could not be done due to bleeding and surgical intervention high risk" for 1 patient each. ITT=intent-to-treat; TURBT=transurethral resection of bladder tumor.
Source: BL006-CSR-Table 14.1.4.2

### *Summary of Efficacy – ITT Analysis Population (ATLAS)*

The DFS sensitivity analysis (as discussed in Section 2.3.3.3) was also performed on the ITT analysis of the primary endpoint. Treatment with UGN-102 reduced the risk of recurrence, progression, or death by 14% relative to TURBT (hazard ratio = 0.86; 95% CI: 0.59, 1.25). At 15 months after randomization, the probability of remaining event free was 56.1% (95% CI: 47.0%, 64.2%) in the UGN-102 arm and 49.5% (95% CI: 39.6%, 58.6%) in the TURBT arm. A summary of the secondary efficacy endpoints is shown in Table 18.

**Table 18 Summary of Secondary Efficacy Endpoints – ITT Analysis Population (ATLAS)**

| Endpoint | UGN-102 (N=142) | TURBT (N=140) |
|---|---|---|
| **CR rate (ITT analysis set), n/N (%) (95% CI)** | 90/142 (63.4) (54.9, 71.3) | 87/140 (62.1) (53.6, 70.2) |
| **DOR (3-month CR analysis set), KM estimate, % (95% CI)** | | |
| 12 months after 3-month CR | 79.2 (68.6, 86.5) | 69.6 (57.6, 78.9) |
| **DCR rates (3-month CR analysis set), n/N % (95% CI)** | | |
| 3 months after 3-month CR | 83/90 (92.2) (84.6, 96.8) | 64/87 (73.6) (63.0, 82.4) |
| 6 months after 3-month CR | 72/90 (80.0) (70.2, 87.7) | 54/87 (62.1) (51.0, 72.3) |
| 9 months after 3-month CR | 67/90 (74.4) (64.2, 83.1) | 50/87 (57.5) (46.4, 68.0) |
| 12 months after 3-month CR | 65/90 (72.2) (61.8, 81.1) | 49/87 (56.3) (45.3, 66.9) |

CI=confidence interval; CR=complete response; DCR=durable complete response; DOR=duration of response; ITT=intent-to-treat; KM=Kaplan-Meier; TURBT= transurethral resection of bladder tumor.
Source: ISE-Table 14.2.1.1.1; Table 14.2.2.1.2.1; Table 14.2.2.2.1.1

## Appendix 7: Summary of Demographics and Baseline Disease Characteristics – FDA Analysis Population (ENVISION)

### Table 19 Summary of Demographics and Baseline Characteristics – FDA Analysis Population (ENVISION)

| **Characteristic**<br>**Statistic** | **UGN-102**<br>**(N=223)** |
|---|---|
| Age (years) | |
| n | 223 |
| Mean (SD) | 68.6 (11.74) |
| Median (min, max) | 70.0 (30, 92) |
| Age group (years), n (%) | 223 |
| <65 | 75 (33.6) |
| ≥65 to <75 | 66 (29.6) |
| ≥75 to <85 | 70 (31.4) |
| ≥85 | 12 (5.4) |
| Sex, n (%) | 223 |
| Male | 139 (62.3) |
| Female | 84 (37.7) |
| Race, n (%) | 223 |
| American Indian or Alaska Native | 0 |
| Asian | 2 (0.9) |
| Black or African American | 2 (0.9) |
| Native Hawaiian or Other Pacific Islander | 0 |
| White | 218 (97.8) |
| Not reported | 1 (0.4) |
| Ethnicity, n (%) | 223 |
| Hispanic or Latino | 3 (1.3) |
| Not Hispanic or Latino | 220 (98.7) |

Age is calculated from date of birth to date of consent. Percentages are computed using the number of patients with non-missing data as the denominator. For missing data, percentages are computed using N as the denominator. SD=standard deviation.
Source: ISE-FDA Analysis Set-Table 14.1.6.1a

### Table 20 Summary of Baseline Disease Characteristics – FDA Analysis Population (ENVISION)

| **Characteristic**<br>**Statistic** | **UGN-102**<br>**(N=223)**<br>**n (%)** |
|---|---|
| Treatment course (instillations) | 223 |
| 6 | 212 (95.1) |
| <6 | 11 (4.9) |
| Longest tumor diameter (cm)[a] | 218 |
| ≤3 | 204 (93.6) |
| >3 | 14 (6.4) |
| Missing | 5 (2.2) |

| Characteristic<br>Statistic | UGN-102<br>(N=223)<br>n (%) |
|---|---|
| Tumor burden (cm)[b] | 205 |
| ≤3 | 169 (82.4) |
| >3 | 36 (17.6) |
| Missing | 18 (8.1) |
| Tumor count | 222 |
| Single | 34 (15.3) |
| Multiple | 188 (84.7) |
| Missing | 1 (0.4) |
| Previous NMIBC episodes | 223 |
| Yes | 223 (100) |
| No | 0 |
| Previous NMIBC episodes within 1 year of the current diagnosis | 223 |
| Yes | 122 (54.7) |
| No | 101 (45.3) |
| Number of previous NMIBC episodes | 223 |
| 0 | 0 |
| 1 | 137 (61.4) |
| 2 | 38 (17.0) |
| >2 | 48 (21.5) |
| Previous LG-NMIBC episodes | 223 |
| Yes | 223 (100) |
| No | 0 |
| Previous LG-NMIBC episodes within 1 year of the current diagnosis | 223 |
| Yes | 122 (54.7) |
| No | 101 (45.3) |
| Number of previous LG-NMIBC episodes | 223 |
| 0 | 0 |
| 1 | 142 (63.7) |
| 2 | 38 (17.0) |
| >2 | 43 (19.3) |
| Number of prior TURBT to treat NMIBC | 223 |
| 0 | 0 |
| 1 | 144 (64.6) |
| 2 | 36 (16.1) |
| >2 | 43 (19.3) |
| Number of prior TURBT to treat LG-NMIBC | 223 |
| 0 | 0 |
| 1 | 149 (66.8) |
| 2 | 36 (16.1) |
| >2 | 38 (17.0) |
| Smoking history[c] | 223 |
| Non-smoker | 101 (45.3) |
| Smoker | 122 (54.7) |

[a]Longest tumor diameter is defined as the longest diameter among all measurable lesions. [b]Tumor burden (cm) is calculated as the sum of the longest diameters of measurable lesions. [c]Smoker category includes both former and current smokers. Non-smoker category includes “Never.” Percentages are computed using the number of non-missing data as the denominator. For missing data, percentages are computed using N as the denominator.

eCRF=electronic case report form; LG=low-grade; NMIBC=non-muscle invasive bladder cancer; TURBT=transurethral resection of bladder tumor.
Source: ISE-FDA Analysis Set-Table 14.1.6.2a

## Appendix 8: Summary of Demographics and Baseline Disease Characteristics – FDA Analysis Population (ATLAS)

### Table 21 Summary of Demographics and Baseline Characteristics – FDA Analysis Population (ATLAS)

| Characteristic<br>Statistic | UGN-102<br>(N=51) | TURBT<br>(N=57) |
|---|---|---|
| Age (years) | | |
| n | 51 | 57 |
| Mean (SD) | 67.8 (8.45) | 68.4 (9.98) |
| Median (min, max) | 69.0 (45, 85) | 69.0 (47, 88) |
| Age group (years), n (%) | 51 | 57 |
| <65 | 17 (33.3) | 22 (38.6) |
| ≥65 to <75 | 23 (45.1) | 17 (29.8) |
| ≥75 to <85 | 10 (19.6) | 15 (26.3) |
| ≥85 | 1 (2.0) | 3 (5.3) |
| Sex, n (%) | 51 | 57 |
| Male | 37 (72.5) | 37 (64.9) |
| Female | 14 (27.5) | 20 (35.1) |
| Race, n (%) | 51 | 57 |
| American Indian or Alaska native | 0 | 0 |
| Asian | 0 | 0 |
| Black or African American | 0 | 0 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 |
| White | 51 (100) | 57 (100) |
| Not reported | 0 | 0 |
| Ethnicity, n (%) | 51 | 57 |
| Hispanic or Latino | 1 (2.0) | 1 (1.8) |
| Not Hispanic or Latino | 50 (98.0) | 55 (96.5) |
| Not reported | 0 | 1 (1.8) |

Age was calculated from date of consent and date of birth. Percentages were computed using the number of patients in ITT Analysis Population with a response value for a corresponding characteristic as the denominator.
ITT=intent-to-treat; SD=standard deviation; TURBT=transurethral resection of bladder tumor.
Source: ISE-FDA Analysis Set-Table 14.1.2.1a

### Table 22 Summary of Baseline Disease Characteristics – FDA Analysis Population (ATLAS)

| Characteristic<br>Statistic | UGN-102<br>(N=51)<br>n (%) | TURBT<br>(N=57)<br>n (%) |
|---|---|---|
| Treatment course (instillations) | 51 | NA |
| 6 | 47 (92.2) | NA |
| <6 | 4 (7.8) | NA |
| Longest tumor diameter (cm)[a] | 49 | 57 |
| ≤3 | 44 (89.8) | 51 (89.5) |
| >3 | 5 (10.2) | 6 (10.5) |
| Missing | 2 (3.9) | 0 |

| Characteristic<br>Statistic | UGN-102<br>(N=51)<br>n (%) | TURBT<br>(N=57)<br>n (%) |
|---|---|---|
| Tumor burden (cm)[b] | 48 | 52 |
| ≤3 | 36 (75.0) | 37 (71.2) |
| >3 | 12 (25.0) | 15 (28.8) |
| Missing | 3 (5.9) | 5 (8.8) |
| Tumor count | 49 | 52 |
| Single | 15 (30.6) | 15 (28.8) |
| Multiple | 34 (69.4) | 37 (71.2) |
| Missing | 2 (3.9) | 5 (8.8) |
| Previous NMIBC episodes[c] | 51 | 57 |
| Yes | 51 (100) | 57 (100) |
| No | 0 | 0 |
| Previous NMIBC episodes within 1 year of the current diagnosis[c] | 51 | 57 |
| Yes | 33 (64.7) | 34 (59.6) |
| No | 18 (35.3) | 23 (40.4) |
| Number of previous NMIBC episodes[c] | 51 | 57 |
| 0 | 0 | 0 |
| 1 | 26 (51.0) | 28 (49.1) |
| 2 | 11 (21.6) | 11 (19.3) |
| >2 | 14 (27.5) | 18 (31.6) |
| Number of prior TURBT to treat NMIBC[c] | 51 | 57 |
| 0 | 0 | 0 |
| 1 | 26 (51.0) | 30 (52.6) |
| 2 | 13 (25.5) | 11 (19.3) |
| >2 | 12 (23.5) | 16 (28.1) |
| Smoking history[d] | 51 | 57 |
| Non-smoker | 23 (45.1) | 32 (56.1) |
| Smoker | 28 (54.9) | 25 (43.9) |

[a]Longest tumor diameter is the longest diameter among all measurable lesions. [b]Tumor burden is calculated as the sum of the longest diameters of the measurable lesions. [c]Based on data from the Urothelial Carcinoma Medical History eCRF. [d]The smoker category includes both former and current smokers, and the non-smoker category includes "Never." Percentages are computed using the number of non-missing data as the denominator. For missing data, percentages are computed using N as the denominator. eCRF=electronic case report form; NMIBC=non-muscle invasive bladder cancer; TURBT=transurethral resection of bladder tumor.
Source: ISE-FDA Analysis Set-Table 14.1.2.2a

## Appendix 9: Clinical Pharmacology

### Overview of Clinical Pharmacology

Historical pharmacokinetic data are available from the scientific literature for the use of mitomycin as a chemotherapeutic agent given by 4 routes of administration (intravenous, oral, intraperitoneal, and intravesical). Pharmacokinetic data for intravesical administration of UGN-102 are available from 3 clinical studies (BL001, BL004, and OPTIMA II). Collectively, these data demonstrate that intravesical instillation of UGN-102 results in considerably lower systemic exposure to mitomycin than intravenous, oral, or intraperitoneal administration of mitomycin. UGN-102 results in minimal systemic absorption of mitomycin, which is associated with a lower risk of systemic side effects.

## Pharmacokinetics

### *Absorption*

The systemic exposure of mitomycin following instillation of 75 mg of mitomycin as UGN-102 into the bladder was evaluated pre-instillation and hourly for up to 6 hours post-instillation in 6 patients. The concentrations of mitomycin in plasma were variable and ranged from 0.19 to 8.94 ng/mL over the course of treatment. The mean maximum plasma concentration ($C_{max}$) was 2.27 ng/mL, which is <1% of the expected $C_{max}$ after intravenous administration and <1% of the mitomycin plasma concentration known to be associated with myelosuppression (400 ng/mL).

### *Elimination*

Following instillation into the bladder, UGN-102 forms a semisolid gel that disintegrates in the urine and releases mitomycin for up to 6 hours. Mitomycin is eliminated unchanged in the urine.[49] Systemically absorbed mitomycin is rapidly cleared from the serum and approximately 10% is excreted unchanged in the urine.

### *Metabolism*

Mitomycin is metabolized primarily in the liver, but metabolism occurs in other tissues as well. It is believed that the rate of clearance is inversely proportional to the maximal serum concentration because of saturation of the degradative pathways.

## Dose Selection

Data from BL002, BL003, and BL004 support selection of the dosing regimen of UGN-102 evaluated in Phase 2 and Phase 3 efficacy studies (75 mg administered once weekly via intravesical instillation for 6 weeks). BL002 was an open-label study of 37.5 and 75 mg UGN-102, BL003 was a randomized controlled study of 37.5 and 75 mg UGN-102 with 40 mg mitomycin in water as a control, and BL004 was planned as an open-label study of 120, 140, and 160 mg UGN-102 (although the 140- and 160-mg doses were not evaluated, as described below). The dosing regimen in all studies was intravesical instillation once weekly for 6 weeks. While efficacy analyses were exploratory in some of these studies, short-term CRRs were dose-related up to the 75-mg dose. The 120-mg dose did not provide an efficacy advantage over the 75-mg dose and had a higher rate of AEs than the 75-mg dose; therefore, doses higher than 120 mg were not tested.

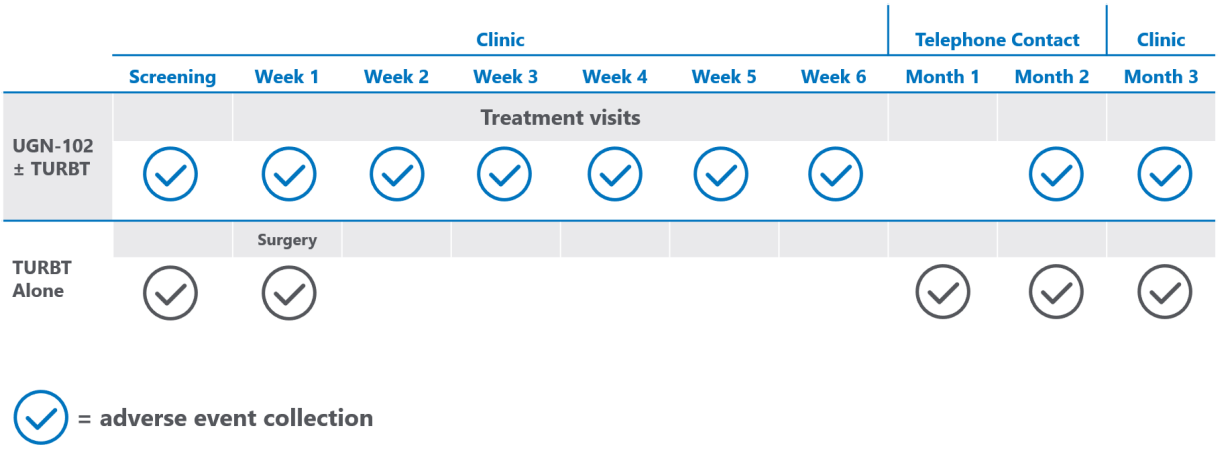
# Appendix 10: Overview of Safety Profile – ATLAS

Comparison of the safety profile between UGN-102 ± TURBT and TURBT alone should be interpreted with caution due to the different schedule of AE collection in the 2 arms of ATLAS, which likely resulted in ascertainment bias and under-reporting of AEs in the TURBT-alone arm.

Patients randomized to UGN-102 were seen in the clinic when they received their 6 weekly instillations and were queried for AEs at each of those clinic visits (Figure 18). In contrast, patients who were randomized to TURBT only attended the clinic at Week 1 to undergo surgery and were not followed for AEs after this visit until telephone contact 1 month later. Both arms

also received telephone contact at Month 2 for AEs and then returned to the clinic at Month 3 for their disease assessment visit. During the Follow-up Period after Month 3, the schedule of AE collection was the same in both arms.

**Figure 19 Schedule of Adverse Event Collection in ATLAS**




After Month 3, the schedule of AE collection was the same in both arms. AE=adverse event; TURBT=transurethral resection of bladder tumor.

### Treatment-Emergent Adverse Events

Overall, 75.4% of patients in the UGN-102 ± TURBT arm experienced TEAEs compared with 47.7% in the TURBT-alone arm (Table 23). The difference between treatment arms was driven by the data from the time period up to 3 months, in which TEAEs occurred in 67.4% and 36.4% of patients, respectively (Table 23). Post 3 months, TEAEs occurred in 33.1% and 28.3% of patients, respectively (Table 23). The rate of TEAEs was comparable between arms in the period post 3 months when AE collection schedules were the same.

Overall treatment-related TEAEs occurred in 39.1% of patients in the UGN-102 ± TURBT arm and 11.4% of patients in the TURBT-alone arm (Table 23). Most of these events were reported in the first 3 months (38.4% and 9.8%, respectively), with fewer events occurring post 3 months (3.0% and 1.7%, respectively) (Table 23). Procedure-related TEAEs occurred in 22.5% of patients in the UGN-102 ± TURBT arm and 1.5% of patients in the TURBT alone arm (Table 23). Most of these events were reported in the first 3 months (20.3% and 1.5%, respectively), with fewer events occurring post 3 months (5.3% and 0%, respectively) (Table 23).

Overall, serious TEAEs occurred in 8.7% of patients in the UGN-102 ± TURBT arm 5.3% of patients in the TURBT-alone arm, and these were more evenly spread across the time periods (Table 23). Up to 3 months, serious TEAEs occurred in 4.3% and 2.3%, respectively (Table 23). Post 3 months, serious TEAEs occurred in 4.5% and 5.0%, respectively (Table 23). Like the overall incidence of TEAEs, serious TEAEs occurred at similar rates during the period post 3 months when AE collection schedules were the same between arms. No patients in the UGN-102 ± TURBT arm and 1 patient (0.8%) in the TURBT-alone arm had a treatment-related serious

TEAE (Table 23). Finally, AESIs occurred in 58% of patients in the UGN-102 ± TURBT arm and 28.8% of patients in the TURBT-alone arm, with most events occurring in the first 3 months (Table 23).

**Table 23 Overall Summary of Adverse Events (ATLAS)**

| | Overall | | Up to 3 Months | | Post 3 Months | |
|---|---|---|---|---|---|---|
| | **UGN-102 ± TURBT (N=138) n (%)** | **TURBT Alone (N=132) n (%)** | **UGN-102 ± TURBT (N=138) n (%)** | **TURBT Alone (N=132) n (%)** | **UGN-102 ± TURBT (N=133) n (%)** | **TURBT Alone (N=120) n (%)** |
| **Any TEAEs** | **104 (75.4)** | **63 (47.7)** | **93 (67.4)** | **48 (36.4)** | **44 (33.1)** | **34 (28.3)** |
| Treatment-related | 54 (39.1) | 15 (11.4) | 53 (38.4) | 13 (9.8) | 4 (3.0) | 2 (1.7) |
| Procedure-related | 31 (22.5) | 2 (1.5) | 28 (20.3) | 2 (1.5) | 7 (5.3) | 0 |
| Any TEAEs leading to treatment discontinuation[a] | 5 (3.6) | N/A | 5 (3.6) | N/A | 0 | N/A |
| Any TEAEs leading to study discontinuation | 4 (2.9) | 2 (1.5) | 3 (2.2) | 0 | 1 (0.8) | 2 (1.7) |
| Any Grade 3 or higher TEAEs | 9 (6.5) | 6 (4.5) | 5 (3.6) | 2 (1.5) | 4 (3.0) | 4 (3.3) |
| Any serious TEAEs | 12 (8.7) | 7 (5.3) | 6 (4.3) | 3 (2.3) | 6 (4.5) | 6 (5.0) |
| Treatment related[b] | 0 | 1 (0.8) | 0 | 1 (0.8) | 0 | 0 |
| Procedure related | 2 (1.4) | 0 | 1 (0.7) | 0 | 1 (0.8) | 0 |
| Any TEAEs leading to death[c] | 0 | 1 (0.8) | 0 | 0 | 0 | 1 (0.8) |
| Any TEAEs of special interest | 80 (58.0) | 38 (28.8) | 73 (52.9) | 27 (20.5) | 20 (15.0) | 17 (14.2) |

[a]AEs leading to treatment discontinuation are only applicable to UGN-102. [b]Treatment-related serious TEAEs occurred in 1 patient in the TURBT-alone arm (hematuria). [c]One death occurred in the TURBT-alone arm (COVID-19). No deaths were considered related to study treatment or procedure. AE=adverse event; N/A=not applicable; TEAE=treatment-emergent adverse event; TURBT=transurethral resection of bladder tumor.
Source: ISS-Table 14.3.1.1.1

### Most Commonly Reported Adverse Events

For the overall study duration, the incidence of TEAEs was highest in the SOC of Renal and Urinary Disorders (52.2% for UGN-102 ± TURBT vs 25.0% for TURBT alone), and this SOC was also the primary driver of the difference between the 2 treatment arms. The individual TEAEs in this SOC with ≥5% higher incidence in the UGN-102 ± TURBT arm compared with the TURBT-alone arm were dysuria (30.4% vs 4.5%), micturition urgency (18.1% vs 7.6%), nocturia (18.1% vs 6.8%), and pollakiuria (15.9% vs 6.1%).

TEAEs of Grade ≥3 in this SOC occurred in 2.2% of patients in the UGN-102 ± TURBT arm and 2.3% of patients in the TURBT-alone arm. Importantly, these clinically relevant AEs occurred at low rates and were balanced between both arms.

### TEAEs Leading to Treatment or Study Discontinuation

TEAEs leading to treatment discontinuation occurred in 5 patients (3.6%) in the UGN-102 ± TURBT arm (Table 23), of whom 2 had treatment-related events (1 patient with dysuria and 1 patient with urinary retention and nocturia). This action is not applicable to the TURBT-alone arm given that all patients in this arm received a single initial TURBT procedure per the study design.

Discontinuation of the study due to TEAEs was infrequent and occurred in 4 patients (2.9%) in the UGN-102 ± TURBT arm, of whom 1 had a treatment-related event (dysuria), and 2 patients (1.5%) in the TURBT-alone arm (Table 23), neither of which was treatment-related.

### Serious Adverse Events

For the overall study duration, serious TEAEs occurred in 12 patients (8.7%) in the UGN-102 ± TURBT arm and 7 patients (5.3%) in the TURBT-alone arm (Table 23). The incidence of serious TEAEs was highest in the SOC of Infections and Infestations (4.3% for UGN-102 ± TURBT vs 3.0% for TURBT alone), with the most common individual serious TEAE being COVID-19 (2.9% vs 1.5%). In the SOC of Renal and Urinary Disorders, serious TEAEs occurred in 2 patients (1.4%) in the UGN-102 ± TURBT arm (1 with urethral stenosis and 1 with urinary retention) and 2 patients (1.5%) in the TURBT-alone arm (both with hematuria). No patients in the UGN-102 ± TURBT arm had a treatment-related serious TEAE. In the TURBT-alone arm, 1 patient (0.8%) had a treatment-related serious TEAE (hematuria), which occurred during the first 3 months (onset Study Day 1).

## Appendix 11: TEAEs Leading to Treatment Discontinuation (Pool 2)

**Table 24 TEAEs Leading to Treatment Discontinuation (Pool 2)**

| **SOC**[a]<br>Preferred Term | **Pool 2**<br>**(N=449)**<br>**n (%)** |
|---|---|
| Patients with any TEAE leading to treatment discontinuation | 19 (4.2)[b] |
| **Renal and Urinary Disorders** | 10 (2.2) |
| Lower urinary tract symptoms | 4 (0.9) |
| Dysuria | 3 (0.7) |
| Urinary retention | 3 (0.7) |
| Micturition urgency | 1 (0.2) |
| Nocturia | 1 (0.2) |
| Urge incontinence | 1 (0.2) |
| **Nervous System Disorders** | 3 (0.7) |
| Cerebrovascular accident | 1 (0.2) |
| Cerebrovascular disorder | 1 (0.2) |
| Intracranial aneurysm | 1 (0.2) |
| Syncope | 1 (0.2) |
| **Cardiac Disorders** | 2 (0.4) |
| Atrial fibrillation | 1 (0.2) |
| Cardiac failure acute | 1 (0.2) |
| Cardiac failure chronic | 1 (0.2) |
| Cardiovascular disorder | 1 (0.2) |
| Mitral valve incompetence | 1 (0.2) |
| Pulmonary valve incompetence | 1 (0.2) |
| Tricuspid valve incompetence | 1 (0.2) |
| **Skin and Subcutaneous Tissue Disorders** | 2 (0.4) |
| Hand dermatitis | 1 (0.2) |
| Rash | 1 (0.2) |

[a]This table displays SOCs where more than 1 patient experienced a TEAE leading to treatment discontinuation.
[b]One additional patient had a TEAE recorded as leading to treatment interruption and study treatment was never resumed (pleural effusion considered not related to study treatment or procedure). AE=adverse event; SOC=system organ class; TEAE=treatment-emergent adverse event.
Source: ISS-Table 14.3.1.9

## Appendix 12: Clinical Laboratory Evaluations, Vital Signs, and Physical Examination Findings

Overall, there was no evidence of a clinically significant adverse impact of UGN-102 on laboratory results. There were no clinically meaningful changes in mean or median values over time across hematology or chemistry parameters in Pool 2. In addition, worsening of hematology or clinical chemistry parameters to CTCAE Grade ≥3 was infrequent (Table 25). In Pool 2, for any given hematology parameter, at most 0.7% of patients had a Grade 3 value and none had a Grade 4 value (Table 25). These data indicate that UGN-102 is not associated with a clinically meaningful risk of bone marrow suppression.

Chemistry results showed that 1.8% of patients in Pool 2 had Grade 3 hyperkalemia (Table 25). However, the predefined analyses of potentially clinically significant laboratory values showed that most potassium elevations were only slightly above the threshold for abnormality (maximum value, 6.6 mmol/L). For all other individual chemistry parameters, at most 0.7% of patients had a Grade 3 value and only 1 patient had a Grade 4 value (increased gamma glutamyl transferase [GGT] in a patient with adenocarcinoma of the pancreas).

Detailed analysis of hepatobiliary laboratory parameters showed that for both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) the incidence of patients with a post-baseline value >3 × upper limit of normal was 0.7% in Pool 2, and there were no cases that met the laboratory criteria for potential Hy's law.

In Pool 2, 26.4% of patients had any grade of creatinine increase from baseline, but few patients had a Grade 3 increase (0.7%) or a potentially clinically significant creatinine level (1.8%) (Table 25). A high percentage of patients had renal impairment at baseline (61.0% Grade 1, 22.1% Grade 2, 0.5% Grade 3), and fluctuations in creatinine are common in patients with renal impairment.

A review of mean and median vital sign values over time revealed no clinically meaningful trends or pattern of changes in Pool 2. Potentially clinically significant vital sign values were infrequent, and no criterion was met by ≥3% of patients.

No patient in Pool 2 had a clinically significant abnormal general physical examination finding at Screening. Urology-oriented physical examinations were performed throughout the studies, and abnormal findings were considered clinically significant for 11 patients. The findings primarily involved the urethral meatus, perineal skin, and mucus membranes.

**Table 25 Laboratory Abnormalities (≥5% All Grades) That Worsened From Baseline**

| Laboratory Abnormality | UGN-102 Pool 2 (N=449) n/N1 (%)[a] | |
|---|---|---|
| | All Grades | Grade ≥3[b] |
| **Hematology** | | |
| Eosinophilia | 69/441 (15.6) | 0/441 |
| Anemia | 72/447 (16.1) | 2/447 (0.4) |
| Lymphocyte count decreased | 63/444 (14.2) | 3/444 (0.7) |
| Neutrophil count decreased | 45/443 (10.2) | 2/443 (0.5) |
| Platelet count decreased | 24/444 (5.4) | 1/444 (0.2) |
| White blood cell count decreased | 35/447 (7.8) | 1/447 (0.2) |
| **Chemistry** | | |
| Alkaline phosphatase increased | 37/444 (8.3) | 1/444 (0.2) |
| ALT increased | 54/443 (12.2) | 2/443 (0.5) |
| AST increased | 49/440 (11.1) | 1/440 (0.2) |
| Blood bilirubin increased | 23/444 (5.2) | 0/444 |
| Creatinine increased | 117/444 (26.4) | 3/444 (0.7) |
| GGT increased | 47/430 (10.9) | 2/430 (0.5) |
| Hyperkalemia | 116/437 (26.5) | 8/437 (1.8) |
| Hyponatremia | 23/439 (5.2) | 0/439 |

[a]The denominator (N1) used to calculate percentage for each row is the number of patients with non-missing laboratory values at baseline and at the specified planned time. [b]The only Grade 4 laboratory abnormality was increased GGT in 1 patient. ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase.
Source: ISS-Table 14.3.4.1.2; Table 14.3.4.2.2

## Appendix 13: Patient-Reported Outcomes

### PRO Measures

The PROs assessed in the UGN-102 trials included the EORTC QLQ-NMIBC24 in all 3 trials (exploratory endpoint in ENVISION and OPTIMA II, secondary endpoint in ATLAS) and the EORTC QLQ-C30 as an exploratory endpoint in ENVISION.

The EORTC QLQ-NMIBC24 assesses symptoms specific to NMIBC and its treatments.[58] The questionnaire consists of 24 items across 11 domains, including 2 functional scales/items (sexual function and sexual enjoyment) and 9 symptom scales/items (urinary symptoms, malaise, intravesical treatment issues, future worries, bloating and flatulence, male sexual problems, sexual intimacy, risk of contaminating a partner, and female sexual problems). For each scale or single item, patients are asked the extent to which they had experienced the symptoms or problems on a 4-point scale (1, not at all; 2, a little; 3, quite a bit; or 4, very much). Patients are asked to consider the past week when responding to each item, or the past 4 weeks for items in the sexual function scale. All responses are linearly transformed to a score ranging from 0 to 100, with higher scores representing worse functioning on the functional scales/items and worse symptoms on symptom scales/items. A positive change from baseline (CFB) represents worsening in functioning on the functional scales/items or worsening symptoms for symptom scales/items.

The EORTC QLQ-C30 consists of both multi-item scales and single-item measures.[59] There are 30 items across 5 functional scales (physical, role, cognitive, emotional, and social functioning), a global health status/QoL scale, and 9 symptom scales/items (fatigue, pain, nausea/vomiting, constipation, diarrhea, sleep, dyspnea, appetite, financial). Patients are asked to consider the past week when responding to each item. The scales and single-item measures range in score from 0 to 100. Higher scores represent better QoL on the global health status/QoL scale, better functioning on functional scales, and more severe symptoms/worse problems on symptom scales/items. A positive CFB for the global health status/QoL scale or functional scales represents an improvement in QoL or functioning, respectively. A positive CFB on symptom scales/items represents worsening symptoms/problems.

### Statistical Analysis

The PROs were analyzed in a descriptive manner, with no statistical comparisons conducted between the 3 trials (ENVISION, OPTIMA II, and ATLAS) or between arms in ATLAS, or between baseline scores and post-baseline scores.

### Limitations

The main limitation of the PROs collected in ENVISION, OPTIMA II, and ATLAS is that responses were collected in a descriptive manner with no formal statistical testing performed. Regardless, the conclusions that can be drawn from these measures are clinically meaningful and importantly demonstrate that UGN-102 did not worsen symptoms, functioning, or QoL for patients. Additional limitations include the single-arm trial design of ENVISION and OPTIMA II, in that there was no comparison to SoC; however, PROs were also collected in both the UGN-102 and TURBT arms of ATLAS. Finally, the patients followed for PRO assessment differed between the trials. In ENVISION and OPTIMA II, PROs were not collected beyond 3 months in patients who did not achieve a CR. During the Follow-up Period in ATLAS, the EORTC QLQ-NMIBC24 was collected in all patients regardless of CR or NCR at the 3-month Visit.