2 SYNOPSIS

Name of Sponsor/Company: UroGen Pharma Ltd.	Individual Study Table Referring to Part of the Dossier: Not applicable	(For National Authority Use only)
Name of Finished Product: UGN-102 (mitomycin) for intravesical solution		
Name of Active Ingredient: Mitomycin		

Title of Study: A Randomized, Controlled, Open-label Study of the Efficacy, Durability, and Safety of UGN-102 With or Without TURBT in Patients With Low Grade Intermediate Risk Non-Muscle Invasive Bladder Cancer (LG IR NMIBC)

Coordinating Investigator:

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Study Centers: A total of 79 sites consented and screened patients, and 72 sites in 10 countries randomized patients into the study, including sites in Bulgaria (9 sites), Estonia (5 sites), Georgia (6 sites), Israel (1 site), Latvia (4 sites), Poland (2 sites), Russia (20 sites), Serbia (2 sites), Ukraine (13 sites), and the United States (10 sites).

Publication (Reference):

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

Study Period (Years):	**Phase of Development:**
12 Jan 2021 (first patient consented) to 17 Mar 2023 (last patient completed) Early Termination: 10 Nov 2021 (early study enrollment closure) and 05 Jan 2023 (sponsor decision to terminate follow-up after the last patient reached the 15-month Visit)	Phase 3

Objectives and Endpoints:

Objective	**Endpoint**
Primary	
To evaluate the efficacy of UGN-102 with or without TURBT vs TURBT alone with respect to DFS in patients with LG IR NMIBC	DFS is 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 assessment after the TURBT procedure • Recurrence of LG disease after the 3-month assessment (ie, during the Follow-up Period) • Progression to HG disease • Death due to any cause

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Objective	**Endpoint**
Secondary	
1) To evaluate the efficacy of UGN-102 with or without TURBT vs TURBT alone with respect to: a) TTR b) CRR at 3-month disease assessment c) DOR d) Avoidance of surgery (TURBT) for treatment of LG IR NMIBC	1) The following efficacy endpoints were evaluated: a) TTR, defined as the time from randomization until the earliest date of recurrence of LG disease or progression to HG disease b) CRR, defined as the proportion of patients who achieved CR at the 3-month disease assessment c) DOR, defined as the time from first documented CR until the earliest date of any of the following events: • Recurrence of LG disease • Progression to HG disease • Death due to any cause d) Proportion of patients requiring TURBT in each arm and average number of TURBT interventions per patient in each arm
2) To evaluate the safety profile of UGN-102 with or without TURBT vs TURBT alone	2) The safety profile of UGN-102 and TURBT were evaluated through standard clinical and laboratory tests (eg, hematology and chemistry, urinalysis, physical examination, vital sign measurements) and through the collection of reports of AEs and SAEs including AEs of special interest
3) To assess the effect of UGN-102 with or without TURBT vs TURBT alone on PROs including disease related symptoms, functioning, and HRQoL	3) Changes from baseline in HRQoL measures assessed by EORTC QLQ-NMIBC24
4) To evaluate visit level CRR	4) Observed CRR at scheduled disease assessment time points, defined as the proportion of patients who had CR at the 3-month disease assessment and maintained CR up to that particular follow-up disease assessment
Exploratory	
To explore potential differences in health resource utilization with UGN-102 vs TURBT in patients with LG NMIBC	Number of patients hospitalized for non-elective reasons, total number and length of non-elective hospitalizations

AE = adverse event; CR = complete response; CRR = complete response rate; DFS = disease-free survival; DOR = duration of response; EORTC = European Organisation for Research and Treatment of Cancer; HG = high grade; HRQoL = health-related quality of life; LG = low grade; LG IR NMIBC = low grade intermediate risk non-muscle invasive bladder cancer; PRO = patient reported outcome; QLQ-NMIBC24 = Quality of Life Questionnaire for NMIBC; SAE = serious adverse event; TTR = time to recurrence; TURBT = transurethral resection of bladder tumor.

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Methodology:

This global Phase 3, randomized, controlled, open-label study was designed to assess the long-term efficacy and safety of UGN-102 with or without transurethral resection of bladder tumor (TURBT) vs TURBT alone for the treatment of patients with LG IR NMIBC.

Eligible patients were randomized in a 1:1 ratio to UGN-102 with or without TURBT or TURBT alone. Randomization was stratified by the presence of a previous LG NMIBC episode within 1 year of the current diagnosis at the initial Screening Visit (yes or no). Starting on Day 1, patients randomized to the UGN-102 arm received 6 weekly intravesical instillations of UGN-102, 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 complete response (CR), defined as having no detectable disease (NDD) in the bladder, received no further treatment and entered the Follow-up Period of the study. Patients confirmed to have a non-complete response (NCR) due to residual low grade (LG) disease in either treatment arm underwent TURBT of any remaining lesions and then entered the Follow-up Period of the study. 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 returned to the clinic every 3 months until the end of their participation in the study to determine if they remained disease free. Patients determined to be disease free remained on study until completion of all follow-up visits or until disease recurrence, disease progression, or death was documented, whichever occurred first. Patients determined to have a protocol-defined recurrence or progression at any follow-up or unscheduled visit were considered to have completed the study and released to the care of their treating physician.

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 reached an endpoint of disease recurrence, progression, or death. Note: The study was originally designed to follow patients for up to 24 months after the start of treatment but following early study enrollment closure (see Number of Patients [Planned and Analyzed]), UroGen terminated the study after the last patient reached the 15-month Visit. These decisions were made to pursue an alternative development strategy for UGN-102 and without knowledge of post-randomization data.

Number of Patients (Planned and Analyzed):

Approximately 632 patients were planned to be enrolled. UroGen stopped study enrollment early after 282 patients were randomized (142 in the UGN-102 ± TURBT arm and 140 in the TURBT alone arm).

Diagnosis and Main Criteria for Inclusion:

Patients ≥ 18 years of age who had:

- Newly diagnosed or historic LG NMIBC (Ta) histologically confirmed by cold cup biopsy at Screening or within 8 weeks of Screening;
- Intermediate risk disease, defined as having 1 or 2 of the following: presence of multiple tumors, solitary tumor > 3 cm, or recurrence (≥ 1 occurrence of LG NMIBC within 1 year of the current diagnosis at the initial Screening Visit);
- Negative voiding cytology for high grade (HG) disease within 6 weeks of Screening;
- Adequate organ and bone marrow function as determined by routine laboratory tests; and
- No evidence of active urinary tract infection (UTI).

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Test Product, Dose and Mode of Administration, Batch Numbers:

Patients randomized to the UGN-102 arm received 6 weekly intravesical instillations of UGN-102. UGN-102 for intravesical instillations contains 75 mg mitomycin in 56 mL admixture (1.33 mg mitomycin per mL). Following evaluation of response at 3 months after the start of treatment, patients confirmed to have an NCR due to residual LG disease underwent TURBT of any remaining lesions.

The UGN-102 labeled drug lots dispensed to patients in this study were BE20800554, BE20800557, BE21800002, BE21800050, BE21800098, BE21800312, and BE21800317.

Duration of Treatment: 6 weeks

Reference Therapy, Dose and Mode of Administration:

There was no reference drug in the study. Patients randomized to the control arm (TURBT alone) underwent TURBT surgery on Day 1.

Following evaluation of response at 3 months after the start of treatment, patients confirmed to have an NCR due to residual LG disease underwent repeat TURBT of any remaining lesions.

Criteria for Evaluation:

Efficacy: Response to treatment was determined based on visual observation (white light cystoscopy), histopathology of any remaining or new lesions by central pathology lab (if applicable), and voiding urine cytology by central pathology lab. Any lesions or suspect tissues were to be biopsied to exclude recurrence.

Safety: The safety of study treatment was assessed by evaluation of adverse events (AEs) (eg, frequency, seriousness, severity, and type), including treatment-emergent AEs of special interest (AESIs), changes from baseline in laboratory values and incidence of measurements defined as potentially clinically significant (PCS), and clinically meaningful changes in physical examination findings including vital signs.

Statistical Methods:

Analysis Populations:

- Intent-to-treat (ITT): All randomized patients; patients were analyzed according to the treatment and strata they were assigned during randomization. Efficacy analyses were conducted using this analysis set.
- Safety analysis set: All patients who received any dose of UGN-102 (treatment arm) or at least one TURBT intervention (control arm); patients were analyzed according to the study treatment they actually received. Safety analyses were conducted using this analysis set.
- Per protocol set (PPS): The subset of patients in the ITT analysis set without major protocol deviations (determined before database lock) that would confound the efficacy evaluation. Selected efficacy analyses were conducted using this analysis set.
- 3-month CR analysis set: All patients from the ITT analysis set who achieved CR at the 3-month disease assessment. Selected efficacy analyses were conducted using this analysis set.

Interim Analysis:

Originally, 2 interim efficacy analyses of the primary endpoint disease-free survival (DFS) were planned when approximately 50% and 75% of the targeted number of DFS events had been documented. Following early study enrollment closure, formal hypothesis testing was removed from the statistical analysis plan (SAP) and no interim analysis was conducted.

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Primary Endpoint:

The primary efficacy endpoint DFS was analyzed in the ITT analysis set. The distribution of DFS was estimated using the Kaplan-Meier method. Median DFS, first and third quartiles, and 95% confidence intervals (CIs) were presented by treatment arm. A stratified Cox regression model was used to estimate the hazard ratio (HR) of DFS, along with 95% CIs. No p-value was generated and no statistical conclusion was made.

Non-complete response (ie, residual disease) at the 3-month disease assessment in the UGN-102 ± TURBT treatment arm was not considered a DFS event because treatment failure is not an event in a neoadjuvant setting. However, having residual disease at the 3-month disease assessment after the TURBT procedure (ie, in the TURBT arm) was considered a DFS event. Progression to HG disease any time during the study (even at the 3-month disease assessment) was considered a DFS event in both arms.

A sensitivity analysis of DFS was performed using data from the PPS.

Subgroup analyses of DFS were performed based on various demographic factors and disease-related characteristics (eg, tumor size and count, previous LG NMIBC episodes, and prior TURBT) and are presented in the body of the clinical study report.

Secondary Endpoints:

- Time to recurrence (TTR) in the ITT analysis set was analyzed according to methodology similar to that described for DFS.
- Complete response rate (CRR) in the ITT analysis set: CRR was presented by treatment arm along with the exact 95% CI. A test for binomial proportions (SAS PROC FREQ with binomial option) was used to derive the exact two-sided 95% CI for the CRR using the Clopper-Pearson method. This analysis also was performed in a subgroup of patients who had at least 1 prior episode of LG NMIBC treated with TURBT.
- Visit level CRR in the 3-month CR analysis set: Observed CRR was presented with nominal 95% exact CI (Clopper-Pearson) for each treatment arm at each scheduled time point (eg, 6-, 9-, 12- and 15-month Visits). This analysis also was performed in a subgroup of patients who had at least 1 prior episode of LG NMIBC treated with TURBT.
- Duration of response (DOR) in the 3-month CR analysis set was analyzed according to methodology similar to that described for DFS. This analysis also was performed in a subgroup of patients who had at least 1 prior episode of LG NMIBC treated with TURBT.
- Avoidance of surgery (TURBT) for treatment of LG IR NMIBC in the safety analysis set: The proportion of patients requiring TURBT in each arm and the average number of TURBT interventions per patient in each arm was summarized.
- Health-related quality of life (HRQoL) in the safety analysis set: Observed values and changes from baseline for the 11 domain scores of the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire for NMIBC (QLQ-NMIBC24) were summarized.

Exploratory endpoints are presented in the body of the clinical study report.

Safety Analysis:

Safety analyses were based on the safety analysis set and included summaries of treatment-emergent AEs (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, lower urinary tract symptoms, voiding interruption due to urethral/penile edema unrelated to prostatic hypertrophy), clinical laboratory assessments, vital signs, physical examinations, and urology-oriented examinations.

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Results:

Patient Disposition:

A total of 282 patients (142 in the UGN-102 ± TURBT arm and 140 in the TURBT alone arm) were randomized (ITT analysis set).

Among randomized patients, 86.6% in the UGN-102 ± TURBT arm and 75.7% in the TURBT alone arm completed the study, most of whom remained in the study through the time of study closure.

A total of 270 patients (138 in the UGN-102 ± TURBT arm and 132 in the TURBT alone arm) received study treatment (safety analysis set). Among the 138 patients treated in the UGN-102 ± TURBT arm, 132 (95.7%) received all 6 planned instillations.

The PPS included 138 patients (97.2%) in UGN-102 ± TURBT arm and 134 patients (95.7%) in the TURBT alone arm. The 3-month CR analysis set included 92 patients (64.8%) in the UGN-102 ± TURBT arm and 89 patients (63.6%) in the TURBT alone arm.

Key Demographics and Baseline Characteristics:

The median age of patients was 68 (range: 23 to 85) years in the UGN-102 ± TURBT arm and 67 (range: 29 to 88) years in the TURBT alone arm. The proportion of male patients was slightly higher in the UGN-102 ± TURBT arm (73.9%) compared to the TURBT alone arm (66.4%). Disease-related characteristics in the UGN-102 ± TURBT and TURBT alone arms, respectively, included: previous LG NMIBC episodes within 1 year (28.9% and 28.6%), prior TURBT (36.6% and 45.7%), baseline tumor size > 3 cm (47.2% and 42.1%), and multiple baseline tumors (57.7% and 67.1%).

Efficacy Results:

Primary Endpoint - Disease-free Survival

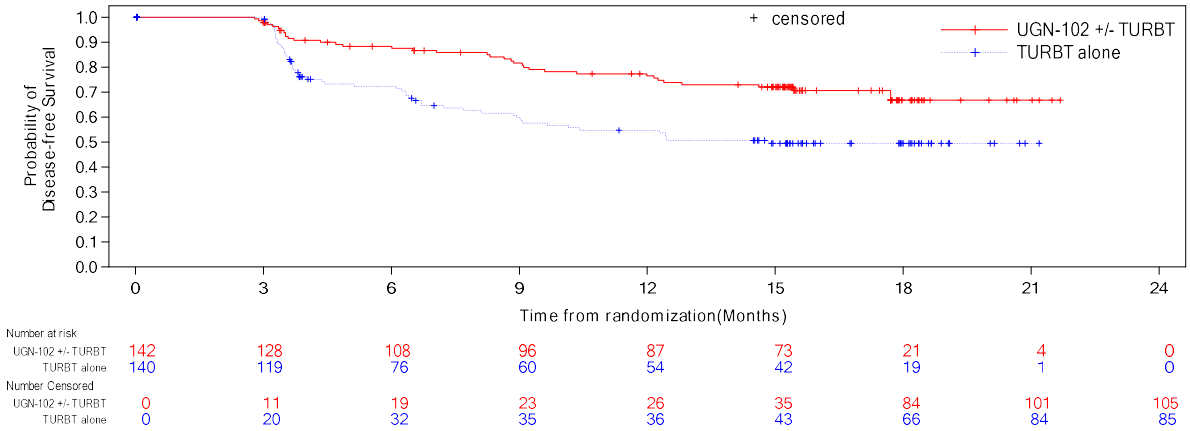
Thirty-seven patients (26.1%) in the UGN-102 ± TURBT arm and 55 patients (39.3%) in the TURBT alone arm had a DFS event (recurrence [including residual disease at the 3-month assessment in the TURBT alone arm], progression, or death). Most of the DFS events were attributable to recurrence of LG disease (14.1% in the UGN-102 ± TURBT arm and 27.9% in the TURBT alone arm). A similar percentage of patients in both arms had progression to HG disease (12.0% and 10.7%, respectively), and there was 1 patient death (0.7%) in the TURBT alone arm.

DFS results indicate that treatment with UGN-102 ± TURBT decreased the risk of recurrence, progression, or death by 55% compared to TURBT alone (HR = 0.45; 95% CI: 0.29, 0.68).

The Kaplan-Meier median DFS was not estimable in the UGN-102 ± TURBT arm and 14.85 months in the TURBT alone arm. Median follow-up time for DFS was 15.41 months in the UGN-102 ± TURBT arm and 15.34 months in the TURBT alone arm.

The estimated probability of remaining event-free at 15 months from randomization was higher in the UGN-102 ± TURBT arm (72.0%; 95% CI: 63.1%, 79.2%) compared to the TURBT alone arm (49.5%; 95% CI: 39.6%, 58.6%).

Kaplan-Meier Plot of Disease-free Survival - ITT Analysis Set



Number at risk									
UGN-102 +/- TURBT	142	128	108	96	87	73	21	4	0
TURBT alone	140	119	76	60	54	42	19	1	0
Number Censored									
UGN-102 +/- TURBT	0	11	19	23	26	35	84	101	105
TURBT alone	0	20	32	35	36	43	66	84	85

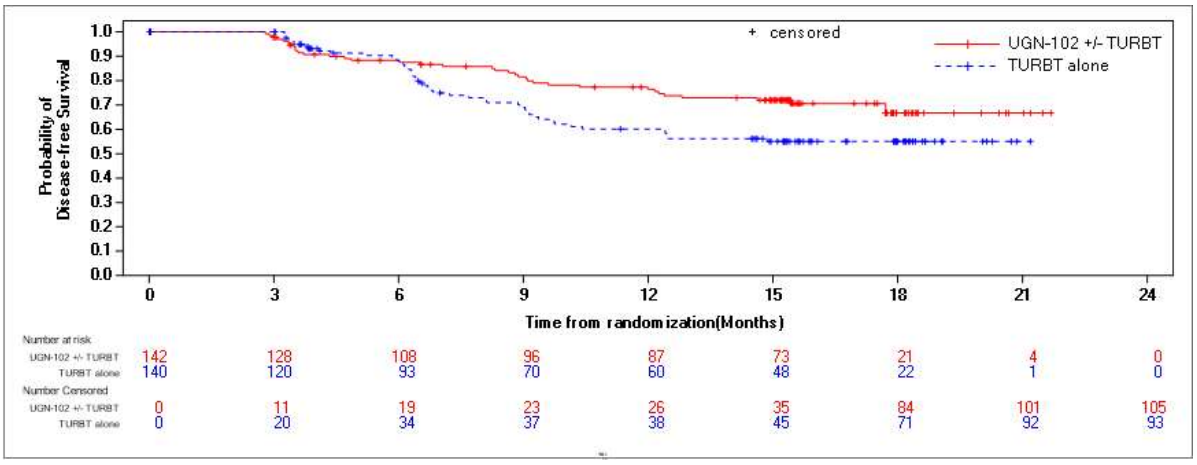
Prespecified Sensitivity Analysis of DFS

Sensitivity analysis of DFS using data from the PPS yielded results similar to the primary analysis.

Post hoc Sensitivity Analyses of DFS

The post hoc principal sensitivity analysis of DFS, in which presence of residual LG disease at 3 months was not treated as a DFS event in either arm (HR = 0.59; 95% CI: 0.38, 0.91), confirmed the robust effect of UGN-102 ± TURBT on the primary endpoint compared to TURBT alone.

Principal Sensitivity Analysis: Summary of Disease-free Survival - ITT Analysis Set



Number at risk									
UGN-102 +/- TURBT	142	128	108	96	87	73	21	4	0
TURBT alone	140	120	93	70	60	48	22	1	0
Number Censored									
UGN-102 +/- TURBT	0	11	19	23	26	35	84	101	105
TURBT alone	0	20	34	37	38	45	71	92	93

An additional post hoc sensitivity analysis of DFS, in which presence of residual LG disease at 3 months was treated as a DFS event in both arms, indicated a HR of 0.86 (95% CI: 0.59, 1.25) favoring the UGN-102 ± TURBT arm.

Secondary Endpoints:

Time to Recurrence

The analysis of TTR was the same as DFS except that death was not considered an event in the analysis. Due to the low number of deaths in the study (n = 1 patient in the TURBT alone arm), results of the TTR analysis were nearly identical to DFS.

Complete Response Rate at 3-month Disease Assessment

The CR rate at 3 months after the start of treatment was similar in both arms and represents a direct comparison of the effects of UGN-102 (64.8%; 95% CI: 56.3, 72.6) versus TURBT (63.6%; 95% CI: 55.0, 71.5).

Analysis in the PPS yielded results similar to the ITT analysis set.

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Duration of Response

UGN-102 had a more durable treatment effect compared to TURBT. Among patients achieving CR at 3 months, DOR results indicate that treatment with UGN-102 decreased the risk of recurrence, progression, or death by 54% compared to TURBT alone (HR = 0.46; 95% CI: 0.24, 0.86) over a median follow-up time of 12.45 months in the UGN-102 ± TURBT arm and 12.16 months in the TURBT alone arm. Like CR rate at 3 months, the DOR results represent a direct comparison of the effects of UGN-102 versus TURBT.

The Kaplan-Meier estimated probability of remaining in response at 12 months after 3-month CR (ie, 15 months after the start of treatment) was higher following treatment with UGN-102 (79.7%; 95% CI: 69.3%, 86.9%) compared to TURBT alone (67.7%; 95% CI: 55.8%, 77.1%).

Visit Level Complete Response Rate

Among patients achieving CR at 3 months, the observed CRR at subsequent disease assessment time points was consistently and meaningfully higher following treatment with UGN-102 compared to TURBT alone. The percentage of patients who maintained CR at the 15-month Visit (ie, 12 months after CR) was 71.7% in the UGN-102 ± TURBT arm and 55.1% in the TURBT alone arm. The higher CRRs at follow-up disease assessments in the UGN-102 arm are notable because patients achieving CR at 3 months received only the primary intervention (UGN-102 or TURBT), with no subsequent surgical intervention such as TURBT.

Avoidance of Surgery (TURBT) for Treatment of LG IR NMIBC

As expected due to similar rates of residual LG disease at the 3-month disease assessment, a similar percentage of patients in both treatment arms underwent procedures for LG NMIBC at 3 months, including TURBT (17.4% in the UGN-102 ± TURBT arm and 13.6% in the TURBT alone arm), office fulguration (0.7% and 1.5%, respectively), or office cold cup biopsy (0.7% and 1.5%, respectively). When combined with the first TURBT for patients in the TURBT alone arm, the mean number of per protocol TURBTs per patient was 0.2 in the UGN-102 ± TURBT arm and 1.1 in the TURBT alone arm.

Health-related Quality of Life

Patient-reported symptoms, functioning, and quality of life as measured by changes from baseline in the EORTC QLQ-NMIBC24 either were improved or not worsened in both the UGN-102 ± TURBT arm and TURBT alone arm.

Safety Results:

Adverse Events

Overall, a total of 104 patients (75.4%) in the UGN-102 ± TURBT arm experienced TEAEs which was higher compared to the TURBT alone arm (63 patients, 47.7%). The difference between treatment arms was driven by the data from the time period up to 3 months, in which TEAEs occurred in 93 patients (67.4%) and 48 patients (36.4%), respectively. Post 3 months, TEAEs occurred in 44 patients (33.1%) and 34 patients (27.4%), respectively. Patients in the UGN-102 arm were queried weekly on-site regarding AEs for the first 6 weeks of the study during instillation visits and via telephone contact at Month 2, whereas patients in the TURBT arm were evaluated at monthly intervals via telephone contact up to the 3-month Visit. This imbalance in evaluation during the first 3 months may have introduced ascertainment bias into the study and underestimated TEAEs associated with TURBT up to the 3-month time point.

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For the overall study duration, the incidence of TEAEs was highest in the system organ class (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 to 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%). The only additional PT with ≥ 5% higher incidence in the UGN-102 ± TURBT arm compared to the TURBT alone arm was flatulence (9.4% vs 3.0%) in the SOC of Gastrointestinal disorders. For the up to 3 months period, the PTs with ≥ 5% higher incidence in the UGN-102 ± TURBT arm compared to the TURBT alone arm were the same as those for the overall study duration. For the post 3 months period, there were no individual PTs with ≥ 5% difference in rates between the treatment arms.

The overall incidence of treatment-related TEAEs was higher in the UGN-102 ± TURBT arm than in the TURBT alone arm (39.1% vs 11.4%). For the time period up to 3 months, the corresponding rates were 38.4% vs 9.8%, and for post 3 months 3.0% vs 1.6%. Similar to the analysis of overall TEAEs, the difference between treatment arms was driven by the SOC of Renal and urinary disorders, including the TEAEs dysuria (24.6% vs 2.3%), micturition urgency (12.3% vs 0.8%), pollakiuria (10.9% vs 2.3%), and nocturia (8.0% vs 1.5%).

Overall, TEAEs related to procedures other than TURBT (eg, cystoscopy, biopsy, MRI, pyelogram, CT urogram, catheter insertion, and cytology) were also reported more frequently in the UGN-102 ± TURBT arm (22.5%) as compared to the TURBT alone arm (1.5%). For the time period up to 3 months, the corresponding rates were 20.3% vs 1.5%, and for post 3 months 5.3% vs 0. In the UGN-102 ± TURBT arm the most frequent procedure-related TEAEs overall were dysuria (8.7%), micturition urgency (4.3%), and pollakiuria (4.3%).

Most patients had TEAEs that were mild to moderate in severity; severe TEAEs occurred at a low rate (6.5% for UGN-102 ± TURBT and 3.8% for TURBT alone). There were no trends noted among the types of severe TEAEs within or between treatment arms.

Serious TEAEs occurred in 12 patients (8.7%) in the UGN-102 ± TURBT arm and 7 patients (5.3%) in the TURBT alone arm. The incidence was highest in the SOC of Infections and infestations, with the most common 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 haematuria). There were no treatment-related serious TEAEs in the UGN-102 ± TURBT arm. In the TURBT alone arm, 1 patient (0.8%) had a treatment-related serious TEAE (haematuria, onset Study Day 1).

There were no deaths in the UGN-102 ± TURBT arm. One death occurred in the TURBT alone arm. This was attributed to COVID-19 (onset Study Day 216) and was assessed as not related to study treatment.

Discontinuation of UGN-102 due to a TEAE occurred in 5 patients (3.6%). These TEAEs corresponded with bladder symptoms in 2 patients (1 with dysuria and 1 with urinary retention and nocturia) and non-urinary conditions in 3 patients (2 with various cardiovascular conditions and 1 with hepatotoxicity). Discontinuation of treatment was not applicable to the TURBT alone arm given that all patients in this arm received a single initial TURBT procedure per the study design.

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TEAEs classified as AESI occurred with a higher incidence in the UGN-102 ± TURBT arm (56.5%) compared to the TURBT alone arm (27.3%). The largest difference between treatment arms was in the category of lower urinary tract symptoms (overall incidence 45.7% vs 20.5%), with findings very similar to the analysis of adverse events in the SOC of Renal and urinary disorders. For the UGN-102 ± TURBT arm, these lower urinary tract symptoms tended to occur within the first 28 days. In the category of voiding interruption due to urethral/penile edema (10.1% vs 3.0%), events in the UGN-102 ± TURBT arm tended to occur more than 28 days after starting treatment. In the category of allergic reactions (7.2% vs 1.5%), most events in the UGN-102 ± TURBT arm were mild to moderate rash or pruritus; events such as the 1 severe event (vulvitis) may have represented mechanical or chemical inflammation following UGN-102 instillation as opposed to true allergic phenomena. The incidence of events in the categories of genitourinary infections and bone marrow suppression was similar between the treatment arms.

Other Safety Assessments

There were no adverse trends in vital signs or laboratory parameters in either treatment arm. One patient discontinued UGN-102 due to a TEAE of hepatotoxicity (maximum alanine aminotransferase [ALT] 6.7 x upper limit of normal [ULN]) that was assessed as not related to treatment by the investigator, had alternate potential etiologies, and subsequently resolved. No patients met Hy's law criteria.

Conclusions:

- Intravesical instillation of UGN-102 once-weekly for 6 weeks with or without TURBT for treatment of patients with LG IR NMIBC demonstrated clinically meaningful improvements in DFS and DOR and a similar 3-month CR rate as compared to TURBT alone.
- TEAEs associated with UGN-102 treatment were predominantly mild to moderate and localized to the lower urinary tract with no reported treatment-related serious AEs.
- Chemoablation with UGN-102 is associated with a favorable benefit-risk profile for the treatment of LG IR NMIBC and may provide a non-surgical alternative to repetitive TURBT surgeries for primary treatment of patients with LG IR NMIBC.

Date of the Report: 28 Nov 2023