Statistical Analysis Plan: BL010

Study Title:	A Phase 3b, Open-Label, Single-Arm, Multicenter Study to Assess the Feasibility of Home Instillation of UGN-102 for Treatment of Patients with Low-Grade (LG) Non-Muscle-Invasive Bladder Cancer (NMIBC) at Intermediate Risk (IR) of Recurrence
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Confidentiality Statement

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
BMI	body mass index
CI	confidence interval
CDISC	clinical data interchange standards consortium
CR	complete response
CRR	complete response rate
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DBP	diastolic blood pressure
eCRF	electronic case report form
EOS	end of study
ET	early termination;
HHP	Home Healthcare Professional
ICH	International Council for Harmonisation
IP	investigational product
IR	intermediate risk
LFT	liver function test
LG	low grade
LLN	lower limit of the normal range
MedDRA	Medical Dictionary for Regulatory Activities
NCR	non-complete response
NMIBC	non-muscle-invasive bladder cancer
PCS	potentially clinically significant
PDP	protocol deviation plan
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan

SAS	Statistical analysis system
SBP	systolic blood pressure
SOA	schedule of activities
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TURBT	transurethral resection of bladder tumors
UC	Urothelial Carcinoma
ULN	upper limit of the normal range

1. INTRODUCTION

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study BL010 (Home Instillation), a phase 3b, open-label, single-arm, multicenter study to assess the feasibility of home instillation of UGN-102 for treatment of patients with low-grade (LG) non-muscle-invasive bladder cancer (NMIBC) at intermediate risk (IR) of recurrence.

This SAP is written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline entitled Structure and Content of Clinical Study Reports (CSR). The SAP is based on the following study documents:

- Protocol, Version 1.0 dated 11 June 2021
- Case report form (CRF), Version 16.4 dated 16 May 2022

All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1 lists the study objectives and corresponding endpoints which are under the scope of this SAP.

Table 1 Study Objectives and Endpoints

OBJECTIVE	ENDPOINT
Primary	
To evaluate the feasibility of home instillation of UGN-102 for treatment of patients with LG IR NMIBC	Feasibility will be assessed by evaluation of: • Safety and tolerability o Reporting of AEs, including SAEs and AESIs o Standard clinical laboratory tests (hematology, serum chemistry, and urinalysis) o Physical examination and vital sign measurements. • Rate of discontinuation from at home study treatment. • Feedback from patients, home health professionals, and investigators via standardized questionnaires
Secondary	
To evaluate the efficacy of UGN-102 for treatment of LG IR NMIBC following home	CRR is defined as the proportion of patients who achieved CR at the 3-month Visit (3 months after the

OBJECTIVE	ENDPOINT
instillation with respect to complete response rate (CRR) at the 3-month disease assessment	first instillation of study treatment) as determined by cystoscopy, for cause biopsy, and urine cytology

AE = adverse event; AESI = adverse event of special interest; CR = complete response; CRR = complete response rate; LG IR NMIBC = low-grade intermediate risk non-muscle-invasive bladder cancer; SAE = serious adverse event.

3. STUDY DESIGN

This Phase 3b, open-label, single-arm, multicenter study is designed to assess the feasibility of home instillation of UGN-102 (mitomycin) for intravesical solution in approximately 10 patients with LG IR NMIBC.

The primary objective of this study is to evaluate the feasibility of home instillation of UGN-102 as an alternative to instillation in a clinical setting. Feasibility will be assessed by evaluation of safety and tolerability, rate of discontinuation from at home study treatment, and feedback from patients, home health professionals, and investigators via standardized questionnaires. The secondary objective of this study is to evaluate the efficacy of UGN-102 for the treatment of LG IR NMIBC following home instillation. Efficacy will be assessed at the 3-month Visit (3 months after the first instillation of UGN-102) by CRR, defined as the proportion of patients who achieved CR as determined by cystoscopy, for cause biopsy, and urine cytology.

Patients who provide informed consent will undergo a Screening Visit to determine eligibility. The Screening Period is up to 14 days for patients who do not need a Screening biopsy and up to 28 days for patients who need a Screening biopsy. Screening procedures are required to provide evidence of LG NMIBC and to rule out evidence of HG disease.

A single representative cold cup biopsy to confirm LG tumor will be performed only if not already performed within 8 weeks before Screening. This is a diagnostic biopsy to demonstrate the histopathology of the tumor, and resection of tumor is not to be performed.

Patients will receive 6 once weekly intravesical instillations of study treatment. The first instillation will be performed at the investigative site and subsequent instillations will be performed at the patient's home by a properly trained and qualified home health professional. The home health professional will call the patient 1 day (+1 day) after each home instillation of study treatment to monitor for safety.

The UGN-102 concentration to be used in this study will be 1.33 mg mitomycin per 1 mL admixture. The volume of UGN-102 admixture to be instilled will be 56 mL (75 mg of mitomycin).

At each home instillation visit, the patient and home health professional will complete a feasibility questionnaire. In addition, the patient and investigator will complete a feasibility questionnaire at the 3-month Visit (EOS) or ET Visit.

Patients will return to the clinic for the 3-monthVisit (7 weeks ± 1 week after the final instillation of UGN-102) for determination of response to treatment.

Response to study treatment will be determined based on visual evaluation by cystoscopy (white light) (appearance, number, and size of any remaining lesions), interpretation of urine cytology, and for cause biopsy and histopathology of any remaining lesions. Any lesions or suspect tissue must be biopsied to evaluate for persistence of disease.

If an unscheduled visit is required during the study, assessments should be performed as appropriate to the needs of the visit.

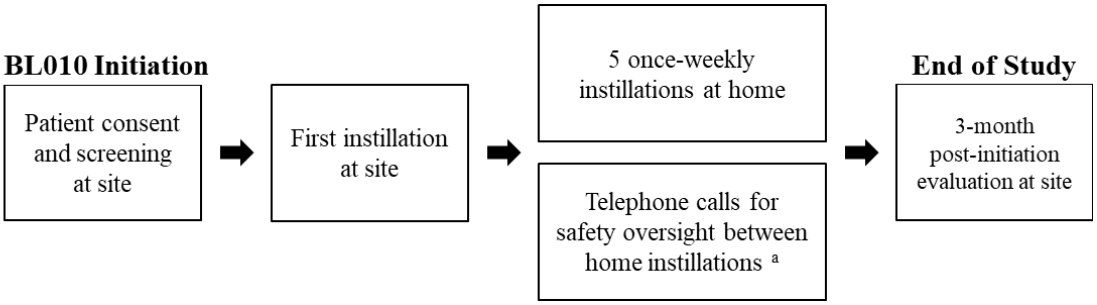
Safety will be evaluated based on vital signs, physical examination, laboratory assessments, and a review of AEs. All safety data will be reviewed on an ongoing basis by the Sponsor, including close review and follow up of any unexpected AE assessed as related to UGN-102, and qualified per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) as Grade 3 or 4.

A patient will be considered to have completed the study if the patient completes the 3-month Visit in accordance with the Schedule of Activities (SoA).

Following the 3-month Visit, all patients will exit the study and continue with standard of care according to their treating physician.

End-of-study is defined as the LPLV. The EOS will be declared after all patients have completed the 3-month Visit.

Figure 1: Study Schema



a. One day after every home instillation (+1 day).

3.1. Statistical Hypothesis

No formal hypothesis will be tested.

3.2. Sample Size Justification

The sample size of this study (approximately 10 patients) is based on feasibility.

3.3. Randomization and Blinding

Not Applicable.

4. PLANNED ANALYSES

4.1. Interim Analyses

No interim analysis is planned for this study.

4.2. Final Analysis

The final analysis will be performed after all patients complete the end of study visit or are withdrawn from the study.

5. ANALYSIS POPULATIONS

For the purposes of analysis, the following analysis set is defined:

Analysis Set	Description
Safety Analysis Set	The Safety Analysis Set includes all patients who received any dose of UGN-102. The Safety Analysis Set will serve as the primary population for the analyses of safety and efficacy data in the study.

6. TREATMENT COMPARISONS

Not Applicable.

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Data will be listed and summarized according to Clinical Data Interchange Standards Consortium (CDISC) standards and ICH E9 Guideline. SAS software will be used to perform all data analyses, generate tables, figures, and listings.

Unless otherwise stated, all listings will be sorted by patient identification number (ID) and then by visit date if applicable.

Unless otherwise stated, continuous variables will be summarized with n, mean, median, standard deviation, minimum and maximum, and categorical variables will be summarized with frequency counts and percentages.

Deviations from the analyses in the SAP will be identified in the CSR.

7.1. Multicenter Studies

Not Applicable.

7.2. Other Strata and Covariates

Not Applicable.

7.3. Multiple Comparisons and Multiplicity

Not applicable.

8. DATA HANDLING CONVENTIONS

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including standard oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

8.1. Premature Withdrawal and Missing Data

A patient will be considered to have withdrawn from the study for any of the following:

- Withdrawal of consent
- Lost to follow-up
- No longer being followed at the Investigator's discretion
- Protocol non-compliance
- Pregnancy
- Patient experienced an AE that led to study discontinuation
- Death
- Study is closed or terminated by the sponsor

If a patient dies or terminates the study prior to the 3-month visit, that patient will be considered as a NCR and will be included in the denominator to calculate the CR rate.

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated using a "blank" in patient listing displays. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Patients with the designation of treatment relationship for adverse events (AE) and serious adverse events (SAEs) missing will have the worst-case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be "Yes." There will be no other imputation for missing data other than what is described in Appendix D Imputation Rules for Missing or Partial Dates.

8.2. Derived and Transformed Data

8.2.1. Reference Date

There are two reference dates:

- The reference date for age is the date of Informed Consent as age is an eligibility requirement.

- The safety/efficacy reference date is the date of first instillation of UGN-102 and will be used to calculate study day for safety/efficacy measures.

8.2.2. Study Day

The study day for safety and efficacy measures are the same in this study. If the date of interest occurs on or after the reference date, then the study day will be calculated as (date of interest - reference date) + 1. If the date of interest occurs before the reference date, then the study day will be calculated as (date of interest – reference date). There is no study day 0.

8.2.3. Calculation of Durations

Durations (e.g., duration of adverse event) will be calculated as stop date minus start date plus one.

8.2.4. Imputation of Partial Dates

In general, imputed partial dates will not be used to derive study day or duration (e.g., duration of adverse events). In addition, imputed dates are not used for deriving the last contact date.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition, partial dates may be imputed for ‘slotting’ data for specific analysis purposes as outlined below.

The partial date imputation will follow Analysis Data Model (ADaM) conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation. The flag variable can contain the values: blank, 'D,' 'M,' 'Y.'

blank: indicates that no imputation was done
D='Day': indicates that the day portion of the date is imputed
M='Month': indicates that the month and day portions of the date are imputed
Y='Year': indicates that the entire date (year, month, and day) is imputed.

Details on imputing partial dates for specific datasets are outlined in Appendix D

8.2.5. Baseline Definition

For Safety analyses, baseline will be defined as the most recent non-missing value prior to the first instillation of UGN-102 i.e., prior to Day 1.

9. PATIENT DISPOSITION, DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Unless otherwise stated, all tables and listings in this section will be based on the safety population, and display the analysis population as 'Safety Analysis Set'.

9.1. Disposition of Patients

The number of patients screened and enrolled will be summarized. In addition, we will also include patients who had at least one UGN-102 instillation and at least one home instillation.

A summary of the number of patients in each of the analysis sets described in Section 5 will be provided.

A summary of treatment status of UGN-102 will be provided. This display will show the number and percentage of patients who discontinued the treatment with the primary reasons for discontinuation. Reasons for treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of UGN-102 treatment discontinuation will be generated.

A summary of patient status of study completion (completed the study versus withdrew/discontinued early) and reasons will be provided. This display will show the number and percentage of patients who completed or withdrew from the study, and primary reasons for study completion/withdrawal. Reasons for study completion/withdrawal will be presented in the order they are displayed in the eCRF. The corresponding listing will also be generated.

9.2. Protocol Deviations

All protocol deviations will be listed and will include severity of the deviation (e.g. major versus minor) and the categories (e.g. eligibility criteria, protocol implementation, safety etc.) using the Safety population. See the Protocol Deviation Plan (PDP) for details of protocol deviations.

9.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g. age, sex, race, ethnicity, height, weight and BMI) will be summarized and listed. Age, height, weight and BMI will be summarized using

the mean, standard deviation, minimum, median (quartiles), and maximum. Categorical variables including but not limited to age group (<65, ≥ 65 to <75, ≥75 to <85, ≥85 years, <65 years versus ≥65 years, and <75 years versus ≥75 years), BMI category (<30 kg/m2, ≥30 kg/m2), sex, race, ethnicity, treatment course (full course - 6 instillations, partial course <6 instillations), tumor size (≤3 cm, >3 cm), tumor count, visual appearance of the lesions, tumor grading, tumor staging, number of prior transurethral resection of bladder tumors (TURBT), Days since the last TURBT and previous LG NMIBC episodes within 1 year of the current diagnosis (Yes, No) will be summarized using counts and percentages.

9.4. General Medical History and Urothelial Carcinoma Related Medical History (UCMH)

Medical history, Past and Concurrent Urothelial Carcinoma (UC) Medical History reported terms will be coded to a SOC and PT using the most recent version of MedDRA dictionary version 24.0 or later. Number and percent of patients reporting any UC related medical history by SOC and PT for the safety analysis set will be provided. A patient with multiple medical conditions will be counted once per SOC and PT. For computing percentages, the denominator will be the number of patients in the SAFETY analysis Set. The summary table will be sorted by descending order of frequency of SOC (then alphabetically for ties), then by descending order of frequency of PT within each SOC (then alphabetically for ties). A patient data listing of medical history will be provided.

9.5. Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary, WHODRUG GLOBAL C3 March 1, 2021 or later. The Anatomical Therapeutic Class (ATC) Level 2, Level 3 and preferred name will be used to list and summarize the data. Analysis of concomitant medications use will be performed in the following manner:

- Prior medications: Any medication that were started and stopped prior to the first instillation of UGN-102. The number and percentage of patients reporting the use of prior medications by ATC Level 2, ATC Level 3 and preferred terms will be summarized for the SAFETY analysis set. For computing percentages, the denominator will be the number of patients in the SAFETY analysis set.
- Concomitant medications: Any prior medications that are ongoing or any new medication administered following the first instillation of UGN-102 for patients in UGN-102 arm. The number and percentage of patients reporting the use of concomitant medications by ATC Level 2, ATC Level 3 and preferred terms will be summarized for the SAFETY analysis set. For computing percentages, the denominator will be the number of patients in the SAFETY analysis set.

All prior and concomitant medications will be included in a data listing.

9.6. Prior and Concomitant Surgical Procedures

Prior surgical procedures are surgical procedures that were done prior to the first instillation of UGN-102 for patients in UGN-102 arm.

Concomitant surgical procedures are surgical procedures that were done following the first instillation of UGN-102 through end of study.

All surgical procedures will be coded to a SOC and PT using the most recent version of the MedDRA dictionary version 23.1 or later. Concomitant surgical procedures will be summarized similar to that described for prior and concomitant medication in Section 9.4.

All prior and concomitant surgical procedures will be included in a data listing.

10. EFFICACY ANALYSES

Efficacy analyses will be based on the SAFETY population as defined in Section 5 or a subset of the SAFETY population as described for each analysis.

Efficacy assessments are based on cystoscopy, for-cause biopsy, and cytology to assess response status of a patient at efficacy visit. Investigator assessments will be considered as primary assessments.

10.1. Efficacy Analyses

10.1.1. Complete Response Rate (CRR) at 3-Month Visit

Complete response rate (CRR) is defined as the proportion of patients in the SAFETY population who achieved CR at the 3-month disease assessment as determined by cystoscopy, for cause biopsy, and urine cytology. If a patient dies or terminates the study prior to the 3-month visit, that patient will be considered as a non-CR and will be included in the denominator to calculate the CR rate.

CRR will be presented along with the exact 95% CIs. A test for binomial proportions (SAS PROC FREQ with binomial option) will be used to derive the exact two-sided 95% CI for the CRR using the Clopper-Pearson method (Clopper and Pearson, 1934).

11. FEEDBACK QUESTIONNAIRE

Feasibility of home instillation will be assessed based on the totality of the data.

11.1. Patient Questionnaire

Patients will be asked to rate their home instillation experience such as comfort, safety/concerns, communication, preference compared to office instillation and overall experience at each home instillation visit after the instillation is completed. A trend in their responses will be measured descriptively. Patients' home instillation

recommendations will also be collected and summarized descriptively at the 3-month Visit/EOS or ET Visit.

Patients home instillation experience questionnaire responses will be summarized by frequency and percentages for each of the domains namely, Comfort, Safety, Communication, Preference and Overall Experience. For computing percentages, the denominator will be the number of patients in the Safety analysis set. A listing of Patient Questionnaire responses will also be presented.

Below table has the scores for each of the questions. The higher score reflects a more favorable response for each of the questions. The scoring method of this questionnaire will consist of a calculation of a raw total score. Each of the domains like Comfort(Q1+Q2+Q3), Safety(Q4), Communication(Q5+Q6), Preference(Q7) and Overall experience score(Q8) will be calculated based on the scoring method in Table 2. In addition, the composite score (sum of all the eight questions scores) will also be calculated based on the table below.

Table 2 Scoring questionnaire responses

		Not at all	**A little**	**Quite a bit**	**Very much**
	Comfort				
1.	Were you more comfortable with today's instillation at home than at your doctor's office?	1	2	3	4
2.	Did you find it more difficult receiving today's instillation at home than at your doctor's office?	4	3	2	1
3.	Did the courtesy and caregiving of the home health professional make you feel comfortable?	1	2	3	4
	Safety				
4.	Did you have any concerns receiving the instillation at home, away from the doctor's office?	4	3	2	1
	Communication				
5.	Did you receive clear and sufficient instructions on what to do and what to expect before the instillation?	1	2	3	4
6.	Did you receive clear and sufficient instructions on what to do and what to expect after the instillation?	1	2	3	4

	Preference				
7.	Did you prefer to have today's instillation done at home compared to the doctor's office?	1	2	3	4
	Overall experience				
8.	Overall are you satisfied with today's instillation performed at home?	1	2	3	4

11.2. Home Healthcare Professional (HHP) Questionnaire

Home health professionals will be asked to complete a set of questionnaires after each home instillation visit. Data will be summarized descriptively. HHP responses will be summarized by frequency and percentages. For computing percentages, the denominator will be the number of patients in the Safety analysis set. A listing of HHP responses will also be presented.

11.3. Investigator Questionnaire

Investigators will be asked to provide their feedback for each patient based on the experiences of the patient and the home health professional(s) at the 3-month Visit/EOS or ET Visit. Investigator responses will be summarized by frequency and percentages. For computing percentages, the denominator will be the number of patients in the Safety analysis set. Listing of Investigator responses will also be presented.

12. SAFETY ANALYSES

The primary analysis is the safety analysis to assess the feasibility of home instillation of UGN-102. All safety analyses will be based on the safety analysis set.

12.1. Extent of Exposure of UGN-102

Treatment exposure of UGN-102 will be categorized as follows:

- 1 instillation of UGN-102
- 2 instillations of UGN-102
- 3 instillations of UGN-102
- 4 instillations of UGN-102
- 5 instillations of UGN-102
- 6 instillations of UGN-102

Categorical treatment exposure will be summarized using patient counts and percentages. For computing percentages, the denominator will be the number of patients in the Safety analysis set.

Descriptive statistics of UGN-102 volume (mL) and mitomycin dose (mg) instilled at week 1 through week 6 will be presented for the Safety analysis set. Mitomycin dose in

mg will be calculated as 1.33 mg/mL concentration of mitomycin times volume of UGN-102 (mL) instilled at week 1 through week 6.

A data listing of treatment exposure will be presented.

Rate of Home instillation Discontinuations:

Any patient who discontinues from the home instillation process will be counted under this category. Descriptive statistics will be used to summarize proportion of patients discontinuing the home instillations. The frequency and the percentages will be presented. For computing percentages, the denominator will be the number of patients in the Safety analysis set.

12.2. Adverse Events

Adverse Events (AEs) will be coded according to the latest version of the MedDRA dictionary version 24.0 or later. AEs will be graded according to the CTCAE Version 5.0.

AEs shall be recorded starting at signing of ICF until the end of the follow-up or early termination. A treatment-emergent adverse event (TEAE) is defined as an AE that occurs on or after the day of the first instillation of UGN-102 or a pre-treatment AE that worsens during the study.

An overall summary with number and percentage of patients with all AEs, all serious AEs (SAE), TEAEs, different TEAE categories, like treatment-related, procedure related, serious, serious related to treatment or procedure, leading to treatment or study discontinuation, fatal, and AEs of special interest (AESI) will be provided.

AEs will be summarized by number and percentage of patients having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A patient with multiple occurrences of an AE will be counted only once in the respective AE category. A patient with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries, the primary SOC will be presented by descending order of frequency in UGN-102 column (alphabetically for ties), then PTs will be sorted by descending order of frequency within each SOC (alphabetically for ties). The sort order for the PT will be based on their frequency.

All AEs will be listed.

12.3. Deaths and Serious Adverse Events

In the event that a patient has withdrawn consent, no data after the withdrawal of consent date from this patient including death is supposed to appear in the database, which should be part of the data cleaning process. All deaths occurring any time from the time of informed consent to the clinical cut-off date will be listed displaying the primary cause of death (Adverse event, related to cancer, or other).

A listing for SAEs will be generated.

12.4. Adverse Events of Special Interest

An adverse event of special interest is a grouping of adverse events that are of scientific and medical concern specific to UGN-102. A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of events.

The following categories of AE of special interest will be summarized by treatment arm as permitted by data:

- Allergic reaction
- Bone marrow suppression
- Genitourinary infections
- Lower urinary tract symptoms
- Voiding interruption due to urethral/penile edema (unrelated to prostatic hypertrophy)

Additional AEs of special interest may be identified through manual review of all AEs by SOC and PT prior to the database lock.

Summaries of the number and percentage of patients with these events will be provided by category and PT; The summary of event characteristics will also be provided, including number of patients with any event, number of events, number of patients with any event that is serious, number of patients with any event that is related to study treatment, the worst outcome of the event, maximum grade and the action taken for the event. The worst-case approach will be applied at patient level for the event outcome, maximum grade and the action taken, i.e. a patient will only be counted once as the worst case from all the events that patient had. These summaries will be provided for each type of AESI separately.

AESIs will be flagged in the general AE listing.

12.5. Clinical Laboratory Evaluations

Samples for hematology, serum chemistry, and urinalysis assessments will be collected according to the SoA table (protocol Section 1.3) and tested at the local laboratory.

12.5.1. Potentially Clinically Significant (PCS) Laboratory Values

Patients with PCS laboratory values will be assessed via the incidence of patients meeting the PCS criteria by time point. For computing percentages, the denominator will be the number of patients with a post-baseline value for the specific laboratory parameter, except for hemoglobin that requires patients with a baseline and a post-baseline value, and the respective time point. The PCS laboratory criteria are provided in Table 3.

Table 3: PCS Laboratory Criteria

Laboratory Parameter	Conventional Unit	Lower Limit	Upper Limit
Chemistry			
Creatinine	mg/dL		>2.2
Sodium	mEq/L	≤130	>150
Potassium	mEq/L	<3.0	>5.5
Total bilirubin	mg/dL		>1.5 × ULN
ALT	U/L		>3 × ULN
AST	U/L		>3 × ULN
GGT	U/L		>2.5 × ULN
Hematology			
Hemoglobin	g/dL	<0.8 × LLN and >20% decrease from baseline	>1.3 × ULN and >30% increase from baseline
Leukocytes	$\times 10^3/\mu L$	≤ 2.8	≥ 16.0
Lymphocytes	$\times 10^3/\mu L$	<0.5	>20
Neutrophils	$\times 10^3/\mu L$	<1.0	
Platelets	$\times 10^3/\mu L$	<75	≥700
ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; PCS = potentially clinically significant; LLN=Lower limit of normal; ULN=Upper limit of normal			

12.5.2. Potentially Clinically Significant Abnormal Liver Function Tests

Patients meeting criteria for abnormal liver function tests (LFTs) by time point will be listed. Threshold values of interest for LFTs are provided in Table 4.

Table 4: Liver Function Tests Criteria

Parameter	Criterion
ALT	>3×ULN; >5×ULN; >10×ULN
AST	>3×ULN; >5×ULN; >10×ULN
ALT and TBL	ALT 3×ULN and TBL >2×ULN
AST and TBL	AST 3×ULN and TBL >2×ULN
ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin; ULN = upper limit of normal	

For a combined criterion to be fulfilled, all conditions have to be fulfilled by the same laboratory measurement. Only patients with newly occurring values (at least one post-baseline measurement and meeting the criterion but not meeting the criterion at baseline) will be counted.

12.6. Vital Signs

Systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, respiration rate and temperature will be measured at Screening and subsequent visits following the SoA table (protocol Section 1.3).

The summary of observed values of the vital sign parameters will be presented at baseline, each planned visit, and worst-case post-baseline (includes both scheduled and unscheduled assessments) as time points. Worst-case values will be presented based on worst minimum and worst maximum values.

A listing of all vital sign assessments along with the change from baseline values, will be produced.

12.6.1. Potentially Clinically Significant (PCS) Vital Sign Abnormalities

PCS criteria will be used to assess PCS vital sign abnormalities. The incidence of patients meeting PCS criteria for pulse rate, SBP, and DBP at baseline, planned visit, and worst-case post-baseline (includes both scheduled and unscheduled assessments) will be provided. For computing percentages, the denominator will be the number of patients with a post-baseline value for the specific vital sign parameter and the respective time point. A listing of patients with PCS vital signs results will also be generated.

The PCS criteria are shown in Table 5.

Table 5: Vital Signs PCS Criteria

Parameter	PCS Criterion
Pulse rate	≤50 bpm ≤50 bpm and decrease of ≥15 bpm from Baseline ≥120 bpm ≥120 bpm and increase of ≥15 bpm from Baseline
Systolic blood pressure	≤90 mmHg ≤90 mmHg and decrease of ≥20 mmHg from Baseline ≥180 mmHg ≥180 mmHg and increase of ≥20 mmHg from Baseline
Diastolic blood pressure	≤50 mmHg ≤50 mmHg and decrease of ≥15 mmHg from Baseline ≥105 mmHg ≥105 mmHg and increase of ≥15 mmHg from Baseline

12.7. General Physical Examination

General physical examination will be performed at the Screening Visit by a physician at the investigative site. Additional full physical examinations may be performed during the study if clinically indicated.

Abnormal results (clinically significant or not clinically significant) will be listed by body system.

12.8. Urology-Oriented Examination

Urology-oriented examinations as described in the Sec 8.3.1 of the protocol, will be performed at screening and subsequent visits following the protocol SoA table (Section 1.3).

A urological examination will be performed at the Screening Visit, Treatment Visit 1, and at the 3-month Visit (or ET) by a physician at the investigative site. Additional urological examinations may be performed during the study if clinically indicated.

A listing of patients with abnormal urology examination findings either clinically significant or not clinically significant will be provided.

13. PHARMACOKINETIC ANALYSES

Not applicable.

14. PHARMACODYNAMIC AND BIOMARKER ANALYS

Not applicable.

15. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

Not applicable.

16. PHARMACOGENETIC DATA ANALYSES

Not applicable.

17. REFERENCES

Brookmeyer R., Crowley J. A Confidence Interval for the Median Survival Time. Biometrics.Vol. 38, 1982:29-41.

18. APPENDICES

Appendix A Patient Questionnaire

The purpose of this questionnaire is for you to share your experience on how you felt receiving UGN-102 intravesical instillation at home. Please indicate the extent to which you felt comfortable and safe with the treatment at home and fill in the questionnaire as per your experience.

Part 1 Must be completed at each home instillation visit after the instillation is completed

		Not at all	**A little**	**Quite a bit**	**Very much**
	Comfort				
1.	Were you more comfortable with today's instillation at home than at your doctor's office?				
2.	Did you find it more difficult receiving today's instillation at home than at your doctor's office?				
	Please explain (free text):				
3.	Did the courtesy and caregiving of the home health professional make you feel comfortable?				
	Safety				
4.	Did you have any concerns receiving the instillation at home, away from the doctor's office?				
	Please explain (free text):				
	Communication				
5.	Did you receive clear and sufficient instructions on what to do and what to expect before the instillation?				
6.	Did you receive clear and sufficient instructions on what to do and what to expect after the instillation?				
	Preference				

7.	Did you prefer to have today's instillation done at home compared to the doctor's office?				
	Please explain (free text):				
	Overall experience				
8.	Overall are you satisfied with today's instillation performed at home?				
	Please explain (free text):				

Part 2 Must be completed at the 3-month Visit (End of Study) or Early Termination Visit

The purpose of this questionnaire is for you to share your recommendation based on your experience on this study.

1. Will you recommend home instillations of UGN-102 for other patients with non-muscle invasive bladder cancer (NMIBC)?

- Yes
- No

Please explain (free text):

2. Will you recommend home instillations of UGN-102 instead of having transurethral resection of bladder tumors (TURBT) for other patients with NMIBC?

- Yes
- No
- Not applicable

Please explain (free text):

Appendix B Home Health Professional Questionnaire

The purpose of this questionnaire is for you to share your experience on how you felt administering UGN-102 intravesical instillation at the patient's home. Please indicate the extent to which you felt comfortable and safe with the treatment at the patient's home and fill in the questionnaire as per your experience.

Part 1 Must be completed at each home instillation visit after the instillation is completed

1. Were you comfortable performing the instillation at this patient's home?
    - Yes
    - No

    Please explain (free text):

2. Was it difficult to perform the instillation at this patient's home?
    - Yes
    - No

    Please explain (free text):

3. Did you have any concerns performing the instillation in the home setting?
    - Yes
    - No

    Please explain (free text):

4. Did you have sufficient support performing the instillation in the home setting?
    - Yes
    - No

    Please explain (free text):

Part 2 Must be completed starting at the second home instillation visit (Treatment Visit 3 onwards)

1. Did you perform the previous home instillation for this patient?
    - Yes
    - No

Appendix C Investigator Questionnaire

Must be completed at the 3-month Visit (End of Study) or Early Termination Visit

The purpose of this questionnaire is to understand how comfortable and safe patients and home health professionals considered home instillation of UGN-102. Please answer the questions below.

1. Was the experience of having your patient receive instillations at home more difficult, less difficult, or not different than having them receive instillation in your office?
    - More difficult
    - Less difficult
    - Not different

    Please explain (free text):
2. How can we improve the overall experience (free text)?

Appendix D Imputation Rules for Missing or Partial Dates

The partial date imputation will follow Analysis Data Model (ADaM) conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation. The flag variable can contain the values: blank, 'D,' 'M,' 'Y.'

blank: indicates that no imputation was done
D='Day': indicates that the day portion of the date is imputed
M='Month': indicates that the month and day portions of the date are imputed
Y='Year': indicates that the entire date (year, month, and day) is imputed.

Details on imputing partial dates for specific datasets are outlined below.

Table 6: Imputation Rules of Adverse Event (AE) Start and End Dates

Dataset	Date	Missing Element	Rule
AE	Start Date	day, month, and year	• No Imputation for completely missing dates
		year	• No Imputation if year is missing
		day, month	• If year of AE start date = year of study treatment start date, then set AE start date = Study treatment start date

			• Else set AE start date = 01JANYYYY • If AE end date is not missing and imputed AE start date > AE end date, then imputed AE start date should be set to AE end date.
		day	• If month and year of start date = month and year of treatment start date, then set AE start date = study treatment start date. • Else set start date = 01MONYYYY. • If AE end date is not missing and imputed AE start date > AE end date, then imputed AE start date should be set to AE end date.
	End Date		• No imputation for partial end dates will be performed

Table 7: Imputation Rules of Prior or Concomitant Medication (CM) Start and End Dates

Dataset	Date	Missing Element	Rule
CM	Start Date	day, month, and year	• No Imputation for completely missing dates
		year	• No Imputation if year is missing
		day, month	• If year of CM start date = year of study treatment start date, then set CM start date = Study treatment start date • Else set CM start date = 01JANYYYY • If imputed CM start date > CM end date (complete or imputed), then imputed CM start date should be set to CM end date.
		day	• If month and year of start date = month and year of treatment start date, then set CM start date = study treatment start date. • Else set start date = 01MONYYYY. • If imputed CM start date > CM end date (complete or imputed), then imputed CM start date should be set to CM end date.
	End Date	year	• No imputation for partial end dates will be performed
		day, month	• Min (Last visit date, 31DECYYYY, Date of Death) • If imputed CM start date > CM end date (complete or imputed), then imputed CM start date should be set to CM end date.

		day	• Min (Last visit date, last day of the month, death day) • If imputed CM start date > CM end date (complete or imputed), then imputed CM start date should be set to CM end date.

Table 8: Imputation Rules of Urothelial Carcinoma (UC) Related Medical History (MH) Start and End Dates

Dataset	Date	Missing Element	Rule (Only impute missing dates for MH related to UC)
MH	Start Date	day, month, and year	• No Imputation for completely missing dates
		year	• No Imputation if year is missing
		day, month	• If year of MH start date = year of start date of the current urothelial carcinoma diagnosis, then set MH start date = min (01JANYYYY, Start date of the current urothelial carcinoma diagnosis -1). • Else if the year of MH start date < year ofstart date of the current urothelial carcinoma diagnosis, then set MH start date = 01JANYYYY. • If imputed MH start date > MH end date (complete or imputed), then imputed MH start date should be set to MH end date.
		day	• If month and year of start date = month and year ofstart date of the current urothelial carcinoma diagnosis, then set MH start date = Start date of the current urothelial carcinoma diagnosis -1. • Else set start date = 01MONYYYY. • If imputed MH start date > MH end date (complete or imputed), then imputed MH start date should be set to MH end date.
	End Date	year	• No imputation for partial end dates will be performed
		day, month	• Min (Start date of the current urothelial carcinoma diagnosis, Last visit date, 31DECYYYY, Date of Death) • If imputed MH start date > MH end date (complete or imputed), then imputed MH start date should be set to MH end date.
		day	• Min (Start date of the current urothelial carcinoma diagnosis, Last visit date, last day of the month, death day)

			• If imputed MH start date > MH end date (complete or imputed), then imputed MH start date should be set to MH end date.

Table 9: Imputation Rules of Prior or Concomitant Surgical Procedures (PR) Start Date

Dataset	Date	Missing Element	Rule
PR	Start Date	day, month, and year	• No Imputation for completely missing dates
		year	• No Imputation if year is missing
		day, month	• If the surgical procedure was performed for a prior history of UC or MH, then do: o If the year of PR start date = year of inform consent date, then set PR start date = min (01JANYYYY, Inform consent date -1). o Else if the year of PR start date < year of inform consent date, then set PR start date = 01JANYYYY. • If the surgical procedure was NOT performed for a prior history of UC or MH, then do: o If year of PR start date = year of study treatment start date, then set PR start date = Study treatment start date -1. o Else set CM start date = 01JANYYYY
		day	• If month and year of PR start date = month and year of treatment start date, then set PR start date = study treatment start date -1. • Else set start date = 01MONYYYY.

Appendix E Laboratory CTCAE Grade Version 5.0 Criteria

Table 10: Laboratory CTCAE Grade Version 5.0 Criteria

Lab Parameter	Conventional Unit	CTCAE Grade v5.0				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin decreased (Anemia)	g/dL	≥LLN	10 – <LLN	8 – <10	< 8	
Hemoglobin increased	g/dL	≤ULN	>ULN – 2 + ULN	>2 + ULN – 4 + ULN	>4 + ULN	
Hypoglycemia (Glucose decreased)	mg/dL	≥LLN	55 – <LLN	40 – <55	30 – <40	<30
Glucose (hyperglycemia)	mg/dL	LLN – ULN	>ULN – 160	>160 – 250	>250 –500	>500
Albumin	g/dL	≥LLN	<LLN – 3	<3 – 2	<2	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase		≤ULN	>ULN – 2.5 × ULN	>2.5 – 5.0 × ULN	>5.0 – 20.0 × ULN	>20.0 × ULN
Alanine aminotransferase increased	U/L	≤ULN	>ULN – 3 × ULN	>3 × ULN – 5 × ULN	>5 × ULN – 20 × ULN	> 20 × ULN
Aspartate aminotransferase increased	U/L	≤ULN	>ULN – 3 × ULN	>3 × ULN – 5 × ULN	>5 × ULN – 20 × ULN	> 20 × ULN
Blood bilirubin increased	mg/dL	≤ULN	>ULN – 1.5 × ULN	>1.5 × ULN – 3 × ULN	>3 × ULN – 10 × ULN	>10 × ULN
Creatinine increased	mg/dL	≤ULN	>ULN – 1.5 × ULN	>1.5 × ULN – 3 × ULN	>3 × ULN – 6 × ULN	>6 × ULN
Calcium (hypocalcemia)	mg/dL	LLN – ULN	<LLN – 8.0	<8.0 – 7.0	<7.0 – 6.0	<6.0

Calcium (hypercalcemia)	mg/dL	LLN – ULN	>ULN – 11.5	>11.5 – 12.5	>12.5 – 13.5	>13.5
Gamma-glutamyl transferase increased	U/L	≤ULN	>ULN – 2.5 × ULN	>2.5 × ULN – 5 × ULN	>5 × ULN – 20 × ULN	> 20 × ULN
Eosinophils increased	$\times 10^3/\mu L$	≤ULN	>ULN and >Baseline			
Lymphocyte count decreased	$\times 10^3/\mu L$	≥LLN	0.8 – < LLN	0.5 – <0.8	0.2 – <0.5	<0.2
Lymphocyte count increased	$\times 10^3/\mu L$	≤4		>4 - 20	>20	
Neutrophil count decreased	$\times 10^3/\mu L$	≥LLN	1.5 – <LLN	1.0 – <1.5	0.5 – <1.0	<0.5
Platelet count decreased	$\times 10^3/\mu L$	≥LLN	75 – <LLN	50 – <75	25 – <50	<25
White blood cell decreased	$\times 10^3/\mu L$	≥LLN	3.0 – <LLN	2.0 – <3.0	1.0 – <2.0	<1.0
White blood cell increased (eukocytosis)	$\times 10^3/\mu L$	≤100			>100	
Hyperkalemia (Potassium increased)	mEq/L	≤ULN	>ULN – 5.5	>5.5 – 6.0	>6.0 – 7.0	>7.0
Hypokalemia (Potassium decreased)	mEq/L	≥LLN	3.0 – <LLN	Symptomatic with 3.0 – <LLN	2.5 – <3.0	<2.5
Hypernatremia (Sodium increased)	mEq/L	≤ULN	>ULN – 150	>150 – 155	>155 – 160	>160
Hyponatremia (Sodium decreased)	mEq/L	≥LLN	130 – <LLN	125 – <130	120 – <125	<120
Notes: ULN = upper limit of normal; LLN = lower limit of normal						

Appendix F Data Display Specifications

The data display specifications are contained in a separate document. The display mock-shells are provided as a guideline - the format and layout may be revised due to potential limitations of the programs and tools used to produce the displays.
The following data displays will be provided for the End of Study analysis.

Table 11: Table of Contents for Data Display Specifications

Type	Section	Number	Title
Table	Patient Info	14.1.1	Summary of Analysis Sets
Table	Patient Info	14.1.2	Summary of Patient Disposition
Table	Patient Info	14.1.3	Summary of Demographics and Baseline Characteristics
Table	Patient Info	14.1.4	Summary of Prior and Concurrent Urothelial Carcinoma Medical Condition
Table	Patient Info	14.1.5	Summary of Concomitant Medications
Table	Patient Info	14.1.6	Summary of Concomitant Surgical Procedures
Table	Efficacy	14.2.1	Summary of Response Rate at the 3-Month Disease Assessment
Table	Feedback Questionnaire	14.2.2.1	Summary of Feedback Questionnaire Observed Scores by
Table	Feedback Questionnaire	14.2.2.2	Summary of Feedback Questionnaire by Home Healthcare Professional (HHP)
Table	Feedback Questionnaire	14.2.2.3	Summary of End of Study Feedback Questionnaire by Patient and Investigator
Table	Safety	14.3.1.1	Overall Summary of Adverse Events
Table	Safety	14.3.1.2	Incidence of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Worst Severity
Table	Safety	14.3.1.3	Incidence of Treatment-Emergent Adverse Events by Preferred Term and Worst Severity
Table	Safety	14.3.1.4	Incidence of Treatment Related Treatment-Emergent Adverse Events by Preferred Term
Table	Safety	14.3.1.5	Incidence of Procedure Related Treatment-Emergent Adverse Events by Preferred Term
Table	Safety	14.3.1.6	Incidence of Treatment Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Table	Safety	14.3.2.1	Incidence of Treatment-Emergent Adverse Events of Special Interest by Category and Preferred Term
Table	Safety	14.3.2.2	Summary of Characteristics of Treatment-Emergent Adverse Event of Special Interest by Category
Table	Safety	14.3.4	Summary of Potentially Clinically Significant Laboratory Values by Time Point
Table	Safety	14.3.5	Summary of Potentially Clinically Significant Vital Signs by Time Point
Table	Safety	14.3.6.1	Summary of Treatment Exposure of UGN-102
Table	Safety	14.3.6.2	UGN-102 Volume (mL) and Mitomycin Dose (mg) by Visit
Listing	Patient Info	16.2.1	Patient Disposition

Listing	Patient Info	16.2.2.1	Protocol Deviation
Listing	Patient Info	16.2.2.2	Patients with Inclusion/Exclusion Criteria Deviations
Listing	Patient Info	16.2.4.1	Demographic and Baseline Characteristics
Listing	Patient Info	16.2.4.2	Medical History
Listing	Patient Info	16.2.4.3	Prior and Concurrent Urothelial Carcinoma Medical Condition
Listing	Patient Info	16.2.4.4	Prior and Concomitant Medications
Listing	Patient Info	16.2.4.5	Prior and Concomitant Surgical Procedures
Listing	Patient Info	16.2.4.6	Prior NMIBC Diagnosis and TURBT History
Listing	Safety	16.2.5	UGN-102 Administration
Listing	Efficacy	16.2.6.1	Visit Level Disease Assessment Based on Cystoscopy, Histopathology, and Cytology
Listing	Feedback Questionnaire	16.2.6.2	Feedback Questionnaire – Patient Questionnaire
Listing	Feedback Questionnaire	16.2.6.3	Feedback Questionnaire – Home Health Professional Questionnaire
Listing	Feedback Questionnaire	16.2.6.4	Feedback Questionnaire – Investigator Questionnaire
Listing	Safety	16.2.7.1	All Adverse Events
Listing	Safety	16.2.7.2	Serious Adverse Events
Listing	Safety	16.2.7.3	Deaths
Listing	Safety	16.2.8.1	Hematology Laboratory Values Lying Outside the Laboratory Reference Ranges
Listing	Safety	16.2.8.2	Chemistry Laboratory Values Lying Outside the Laboratory Reference Ranges
Listing	Safety	16.2.8.3	Urinalysis Laboratory Values
Listing	Safety	16.2.8.4	Potentially Clinically Significant (PCS) Laboratory Values and Abnormal LFT
Listing	Safety	16.2.8.5	Urine Culture
Listing	Safety	16.2.9.1	Vital Signs Results
Listing	Safety	16.2.9.2	Potentially Clinically Significant (PCS) Vital Sign Results
Listing	Safety	16.2.10.1	General Physical Examinations with Abnormal Results
Listing	Safety	16.2.10.2	Urology-Oriented Physical Examinations with Abnormal Results